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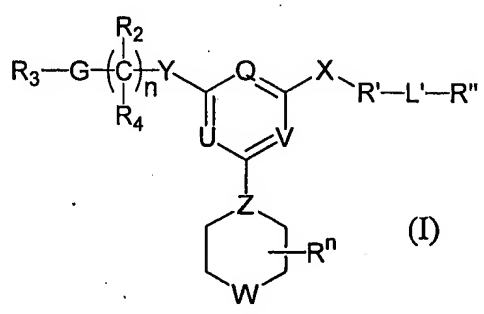
(54) Title: HETEROARYL-HYDRAZONE COMPOUNDS



(I)

(57) Abstract: This invention relates to compounds having a formula (I): or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, prodrug or polymorph thereof wherein X is -C(R[8])=N-A. The invention also relates to methods of treating IL-12 verproduction-related disorders, methods of treating or preventing disorders related with excessive bone loss, methods for inhibiting osteoclast formation, and methods for treating or preventing a disorder associated with excessive bone resorption.

HETEROARYL-HYDRAZONE COMPOUNDS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/518,787, filed November 10, 2003, the entire teachings of which are incorporated herein.

BACKGROUND

Interleukin-12 (IL-12) is a heterodimeric cytokine (p70) which plays key roles in immune responses by bridging innate resistance and antigen-specific adaptive immunity. Trinchieri (1993) *Immunol Today* 14: 335. For example, it promotes type 1 T helper cell (T_H1) responses and, hence, cell-mediated immunity. Chan *et al.* (1991) *J Exp Med* 173: 869; Seder *et al.* (1993) *Proc Natl Acad Sci USA* 90: 10188; Manetti *et al.* (1993) *J Exp Med* 177: 1199; and Hsieh *et al.* (1993) *Science* 260: 547. Interleukin-12 (IL-12) is a di-sulfide linked heterodimeric cytokine (p70) composed of two independently regulated subunits, p35 and p40. IL-12 is produced by phagocytic cells and antigen presenting cells, in particular, macrophages and dendritic cells, upon stimulation with bacteria, bacterial products such as lipopolysaccharide (LPS), and intracellular parasites. The well-documented biological functions of IL-12 are induction of interferon-γ expression from T and NK cells and differentiation toward the T_H1 T lymphocyte type. IFN-γ, expression of which is induced by IL-12, is a strong and selective enhancer of IL-12 production from monocytes and macrophages. The cytokine IL-23 is a heterodimer composed of a p19 subunit and the same p40 subunit of IL-12. IL-23, similarly to IL-12, is involved in type 1 immune defenses and induces IFN-γ secretion from T cells. IL-27 is formed by the association of EBI3, a polypeptide related to the p40 subunit of IL-12, and p28, a protein related to the p35 subunit of IL-12. IL-27 promotes the growth of T cells and is thought to play a role in the differentiation of T_H1 cells. Pflanz *et al.*, *Immunity* (2002), *16*:779-790.

It has been suggested that, particularly in chronic diseases in which there is ongoing production of IFN-γ, IL-12 production is augmented by IFN-γ. It is presumed that after an infective or inflammatory stimulus that provokes IL-12 production, the powerful feedback loop promotes IL-12- and IL-23-induced IFN-γ to further augment IL-12 production, leading to consequent excessive production of pro-inflammatory cytokines. Furthermore, it has been suggested that IL-27 induces the expression of T-bet, a major T_H1-specific transcription factor, and it's downstream target IL-12R β2, independently of IFN-γ. In addition, IL-27 suppresses the expression of GATA-3. GATA-3 inhibits T_H1 development and causes loss of

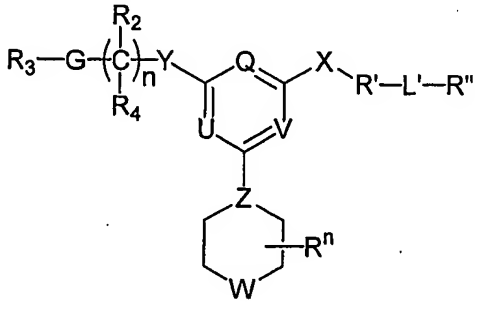
IL-12 signaling through suppression of IL-12R β2 and Stat4 expression. Lucas *et al.*, *PNAS* (2003), *100*:15047-15052.

IL-12 plays a critical role in multiple-T_H1 dominant autoimmune diseases such as multiple sclerosis, sepsis, myasthenia gravis, autoimmune neuropathies, Guillain-Barré syndrome, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, psoriatic arthritis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, ulcerative colitis, interstitial pulmonary fibrosis, myelofibrosis, hepatic fibrosis, myocarditis, thyroditis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland; rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, spondyloarthropathies, ankylosing spondylitis, Sjogren's syndrome and graft-versus-host disease. See, for example, Gately *et al.* (1998) *Annu Rev Immunol.* 16: 495; and Abbas *et al.* (1996) *Nature* 383: 787.

Inhibiting IL-12 overproduction, or inhibiting the production of cytokines such as IL-23 and IL-27 which promote IL-12 production and/or T_H1 development is an approach to treating the just-mentioned diseases. Trembleau *et al.* (1995) *Immmunol. Today* 16: 383; and Adorini *et al.* (1997) *Chem. Immunol.* 68: 175. For example, overproduction of IL-12 and the resultant excessive T_H1 type responses can be suppressed by modulating IL-12, IL-23 and/or IL-27 production. Therefore, compounds that down-regulate IL-12, IL-23 and/or IL-27 production can be used for treating inflammatory diseases. Ma *et al.* (1998) *Eur Cytokine Netw* 9: 54.

SUMMARY

In one aspect this invention relates to compounds having a formula (I):



(I),

or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, prodrug, or polymorph

thereof

wherein, each Q, U, and V are independently N or CR^g, wherein at least one of Q, U, or V is N;

Z is N or CH; W is O, S, S(O), $S(O)_2$, NR^m, or $NC(O)R^m$, wherein R^m is independently H, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or alkylcarbonyl;

X is $-C(R^g)=N-A-$, wherein A is O, S, S(O), $S(O_2)$, $C(CR^g)_2$, or NR^k;

R' is an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, or absent; L' is O, S, $N(R^k)$, $N(R^k)C(O)$, $C(O)N(R^k)$, C(O)O, or OC(O), or absent; and R" is H, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $N(R^k)(CH_2)_nR^g$, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, $-C(O)R^c$, $-C(S)R^c$, $-C(NR)R^c$, halo, haloalkyl, aminoalkyl, mercaptoalkyl, cyano, nitro, $-S(O)R^c$, $-S(O)_2R^c$, $-P(O)R^cR^c$, $-P(S)R^cR^c$, or an optionally substituted alkylcarbonylalkyl;

Y is $(CH(R^g))_m$, C(O), C(NR), O, S, S(O), $S(O)_2$, $N(R^k)$, or absent;

R, for each occurrence, is independently H, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $-C(O)R^c$, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, nitro, cyano, haloalkyl, aminoalkyl, or $-S(O)_2R^c$;

R_3 is R^g, $-C(O)R^c$, $-OC(O)R^c$, $-SC(O)R^c$, $-NR^kC(O)R^c$, $-C(S)R^c$, $-OC(S)R^c$, $-SC(S)R^c$, $-NR^kC(S)R^c$, $-C(NR)R^c$, $-OC(NR)R^c$, $-SC(NR)R^c$, $-NR^kC(NR)R^c$, $-SO_2R^c$, $-S(O)R^c$,$-NR^kSO_2R^c$, $-OS(O)_2R^c$, $-OP(O)R^cR^c$, or $-P(O)R^cR^c$;

R_2 and R_4 for each occurance, are independently, H, an optionally substituted alkyl, an optionally substituted alkylcarbonyl, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, $-C(O)R^c$, $-OC(O)R^c$, $-SC(O)R^c$, $-NR^kC(O)R^c$, $-C(S)R^c$, $-OC(S)R^c$, $-SC(S)R^c$, $-NR^kC(S)R^c$, $-C(NR)R^c$, $-OC(NR)R^c$, $-SC(NR)R^c$, $-NR^kC(NR)R^c$, $-SO_2R^c$, $-S(O)R^c$, $-NR^kSO_2R^c$, $-OS(O)_2R^c$, $-OP(O)R^cR^c$, $-P(O)R^cR^c$, halo, haloalkyl, aminoalkyl, mercaptoalkyl, cyano, nitro, nitroso, azide, an optionally substituted alkylcarbonylalkyl, an optionally substituted cyclyl, an optionally

substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted aralkyl, an optionally substituted heteroaryl, an optionally substituted heteroaralkyl, or isothionitro; or R_2 and R_4 taken together are =O, =S, or =NR;

R^c and R^d, for each occurrence, are independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl, haloalkyl, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, alkylcarbonylalkyl, mercaptoalkyl, aminoalkyl, sulfonylalkyl, sulfonylaryl, or thioalkoxy;

R^g, for each occurrence, is independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl, haloalkyl, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, alkylcarbonylalkyl, mercaptoalkyl, aminoalkyl, sulfonylalkyl, sulfonylaryl, thioalkoxy, $-C(O)R^c$, $-OC(O)R^c$, $-SC(O)R^c$, $-NR^kC(O)R^c$, $-C(S)R^c$, $-OC(S)R^c$, $-SC(S)R^c$, $-NR^kC(S)R^c$, $-C(NR)R^c$, $-OC(NR)R^c$, $-SC(NR)R^c$, $-NR^kC(NR)R^c$, $-SO_2R^c$, $-S(O)R^c$, $-NR^kSO_2R^c$, $-OS(O)_2R^c$, $-OP(O)R^cR^c$, $-P(O)R^cR^c$, halo, cyano, nitro, nitroso, or azide;

R^h and R^j, for each occurrence, are independently H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl; or R^h and R^j taken together with the N to which they are attached is an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, or an optionally substituted heteroaryl;

R^k, for each occurrence, is independently H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl;

R^n is –H, alkyl, alkylcarbonyl, halo, nitro, nitroso, cyano, azido, isothionitro, -OR^p or -SR^p; and R^p is –H, alkyl, or alkylcarbonyl;

G is: Hydrazide (e.g., -C(O)NHN(Rk)- or –N(Rk)NHC(O)-); Hydrazone (e.g., -C(Rg)=N-N(Rk)- or >C=N-NRhRj or –N(Rk)-N=C(Rg)-); Hydrazine (e.g., -N(Rk)-N(Rk)-); Hydroxylamine (i.e., -N(OH)-); Oxime (i.e., -C(N-OH)-); Amide; Ester; Carbonate (-OC(O)O-); Carbamate (e.g., -OC(O)N(Rk)- or –N(Rk)C(O)O-); Thiocarbamate (e.g., -OC(S)N(Rk)- or –N(Rk)C(S)O- or -SC(O)N(Rk)- or –N(Rk)C(O)S-); –NR^k-C(NR)-NR^k-; –NR^k-C(O)-NR^k-; –NR^k-C(S)-NR^k-; -NR^k-$S(O)_2$-NR^k-; Phosphoryl; an optionally substituted -Cyclyl-; an optionally substituted -Heterocyclyl-; an optionally substituted -Aryl-; an optionally substituted -Heteroaryl-; an optionally substituted -Heteroarylalkyl-; an optionally substituted -Heteroaryl-NR^k-; an optionally substituted -Heteroaryl-S-; an optionally substituted -Heteroarylalkyl-O-; -$Si(OR^k)_2$-; -$B(OR^k)$-; -C(NR)-NR^k-; –$N(R^k)$-CR^gR^g-C(O)-; -C(O)-$ON(R^k)$-; -C(O)-$N(R^k)$O-; -C(S)-$ON(R^k)$-; -C(S)-$N(R^k)$O-; -$C(N(R^k))$-$ON(R^k)$-; -$C(N(R^k))$-NR^kO-; -$OS(O)_2$-$N(R^k)N(R^k)$-; -OC(O)-$N(R^k)N(R^k)$-; -OC(S)-$N(R^k)N(R^k)$-; -$OC(N(R^k))$-$N(R^k)N(R^k)$-; -$N(R^k)N(R^k)S(O)_2O$-; -$N(R^k)N(R^k)$C(S)O-; -$N(R^k)N(R^k)C(N(R^k))$O-; -OP(O)(R^c)O-; -$N(R^k)$P(O)(R^c)O-; -OP(O)(R^c)$N(R^k)$-; -$N(R^k)$P(O)(R^c)$N(R^k)$-; -P(O)(R^c)O-; -P(O)(R^c)$N(R^k)$-; -$N(R^k)$P(O)(R^c)-; -OP(O)(R^c)-; -O-alkyl-heterocyclyl-$N(R^k)$-; -$N(R^k)CHR^gC(O)N(R^k)CHR^gC(O)$-; -$N(R^k)CHR^gC(O)$-; -$N(R^k)C(O)CHR^g$-; -C(O)$N(R^k)CHR^gC(O)$-; or absent, each of which is optionally substituted;

m, for each occurrence, is independently 1, 2, 3, 4, 5, 6, 7, or 8; n, for each occurrence, is independently 0, 1, 2, 3, 4, 5, 6, or 7; and p, for each occurrence, is independently 0, 1, or 2.

In one aspect, the invention comprises a pharmaceutical composition comprising a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting the production of IL-12 and/or inhibiting the production of a cytokine that stimulates or augments the production of IL-12 (e.g., IL-23 and IL-27) in a subject by administering to the subject an effective amount of a compound of any of the formulae herein, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

In another aspect, the invention features a method of inhibiting the proliferation and/or development of T_H1 cells in a subject by administering to the subject an effective

amount of a compound of any of the formulae herein, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

In another aspect, the invention provides a method of treating an IL-12 overproduction-related disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the formulae herein or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof. IL-12 overproduction disorders include, but are not limited to multiple sclerosis, sepsis, myasthenia gravis, autoimmune neuropathies, Guillain-Barré syndrome, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, psoriatic arthritis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, ulcerative colitis, interstitial pulmonary fibrosis, myelofibrosis, hepatic fibrosis, myocarditis, thyroditis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland; rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, spondyloarthropathies, ankylosing spondylitis, Sjogren's syndrome and graft-versus-host disease.

In another aspect, the invention provides a method of treating or preventing disorders associated with excessive bone loss, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof. Disorders associated with excessive bone loss include, but are not limited to periodontal disease, non-malignant bone disorders, osteoporosis, Paget's disease of bone, osteogenesis imperfecta, fibrous dysplasia, and primary hyperparathyroidism, estrogen deficiency, inflammatory bone loss, bone malignancy, arthritis, osteopetrosis, hypercalcemia of malignancy (HCM), osteolytic bone lesions of multiple myeloma and osteolytic bone metastases of breast cancer, and metastatic cancers.

In another aspect, the invention provides a method for inhibiting osteoclast formation *in vitro* or *in vivo*, comprising contacting a pre-osteoclast cell with an effective amount of a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

In another aspect, the invention provides a method of treating or preventing a disorder associated with excessive bone resorption by osteoclasts in a subject in need thereof,

comprising administering to the subject an effective amount of a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

DETAILED DESCRIPTION

Embodiments may include one or more of the following features:

Q, U, and V are each N.

Two of Q, U and V can be N, and the other can be CR^g. For example, Q and U each can be N and V can be CR^g; or U and V each can be N, and Q can be CR^g; or Q and V each can be N and U can be CR^g.

One of Q, U and V can be N, and the other two are each CR^g in which each R^g may be the same or different. (e.g., one or both of the other two are CH, preferably both are CH); For example, U can be N, and Q and V can be CR^g, or Q can be N, and U and V can be CR^g, or V can be N and Q and U can be CR^g).

Y is absent, O, S, $N(R^k)$, or CH_2, and n is 0, 1, 2, 3, or 4.

R_3 is an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl, nitro, cyano, halo, OR^k, SR^k, or NR^hR^j. Preferably, R_3 is optionally substituted aryl or optionally substituted heteroaryl. Preferred examples of R_3 include an optionally substituted phenyl, an optionally substituted naphthyl, an optionally substituted anthracenyl, an optionally substituted fluorenyl, an optionally substituted indenyl, an optionally substituted azulenyl, an optionally substituted pyridyl, an optionally substituted 1-oxo-pyridyl, an optionally substituted furanyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted benzo[1,4]dioxinyl, an optionally substituted thienyl, an optionally substituted pyrrolyl, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted thiazolyl, an optionally substituted isoxazolyl, an optionally substituted quinolinyl, an optionally substituted pyrazolyl, an optionally substituted isothiazolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted triazinyl, an optionally substituted triazolyl, an optionally substituted thiadiazolyl, an optionally substituted isoquinolinyl, an optionally substituted indazolyl, an optionally substituted benzoxazolyl, an optionally substituted benzofuryl, an optionally substituted indolizinyl, an optionally substituted imidazopyridyl, an optionally substituted tetrazolyl, an optionally substituted benzimidazolyl, an optionally substituted

benzothiazolyl, an optionally substituted benzothiadiazolyl, an optionally substituted benzoxadiazolyl, an optionally substituted indolyl, an optionally substituted tetrahydroindolyl, an optionally substituted azaindolyl, an optionally substituted indazolyl, an optionally substituted imidazopyridyl, an optionally substituted quinazolinyl, an optionally substituted purinyl, an optionally substituted pyrrolo[2,3]pyrimidinyl, an optionally substituted pyrazolo[3,4]pyrimidinyl, or an optionally substituted benzo(b)thienyl.

In another embodiment, R_3 is an optionally substituted heterocycloalkyl. Preferred embodiments of R_3 include an optionally substituted piperidinyl, an optionally substituted piperazinyl, an optionally substituted 2-oxopiperazinyl, an optionally substituted 2-oxopiperidinyl, an optionally substituted 2-oxopyrrolidinyl, an optionally substituted 4-piperidonyl, an optionally substituted tetrahydropyranyl, an optionally substituted oxazolidinyl, an optionally substituted 2-oxo-oxazolidinyl, an optionally substituted tetrahydrothiopyranyl, an optionally substituted tetrahydrothiopyranyl sulfone, an optionally substituted morpholinyl, an optionally substituted thiomorpholinyl, an optionally substituted thiomorpholinyl sulfoxide, an optionally substituted thiomorpholinyl sulfone, an optionally substituted 1,3-dioxolanyl, an optionally substituted [1,4]dioxanyl, an optionally substituted 2-oxo-imidazolidinyl, tetrahydrofuranyl, or an optionally substituted tetrahydrothienyl.

In another embodiment, R_3 is OR^k, SR^k, $C(O)OR^k$, NR^hR^j, or $C(O)NR^hR^j$. Preferred embodiments of R_3 include $-OR^k$, $-C(O)R^c$, $-OC(O)R^c$, $-NR^kC(O)R^c$ or $-NR^hR^j$, and R^k, R^h and R^j are each, independently, H, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, or an optionally substituted heterocycloalkyl.

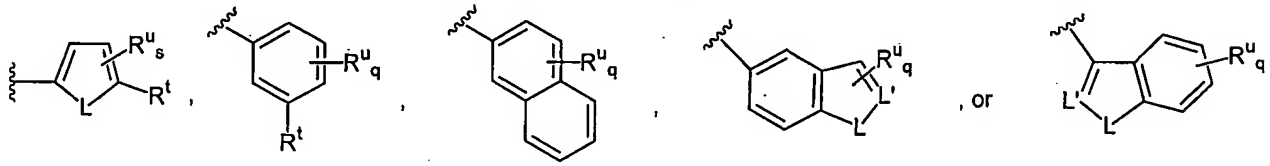
Preferably, G is absent. In another preferred embodiment, G is $-C(N\text{-}OH)-$, $-NR^kC(O)-$, $-C(O)NR^k-$, $-OC(O)-$, $-C(O)O-$, $-OC(O)O-$, $-NR^kC(O)O-$, $-OC(O)NR^k-$, $-NR^kC(S)O-$, $-OC(S)NR^k-$, $-NR^kC(NR)NR^k-$, $-NR^kC(O)NR^k-$, $-NR^kC(S)NR^k-$, $-NR^kS(O)_2NR^k-$, $-C(NR)NR^k-$, or $-NR^kCR^gR^gC(O)-$.

Z is N and W is O.

R" is an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, or an optionally substituted heterocyclyl. Preferably, R" is an optionally substituted aryl or an optionally substituted heteroaryl. In a preferred embodiment, R" is an optionally substituted phenyl, an optionally substituted naphthyl, an optionally substituted anthracenyl, an optionally substituted fluorenyl, an optionally substituted indenyl, an optionally substituted azulenyl, an optionally substituted

pyridyl, an optionally substituted 1-oxo-pyridyl, an optionally substituted furanyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted benzo[1,4]dioxinyl, an optionally substituted thienyl, an optionally substituted pyrrolyl, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted thiazolyl, an optionally substituted isoxazolyl, an optionally substituted quinolinyl, an optionally substituted pyrazolyl, an optionally substituted isothiazolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted triazinyl, an optionally substituted triazolyl, an optionally substituted thiadiazolyl, an optionally substituted isoquinolinyl, an optionally substituted indazolyl, an optionally substituted benzoxazolyl, an optionally substituted benzofuryl, an optionally substituted indolizinyl, an optionally substituted imidazopyridyl, an optionally substituted tetrazolyl, an optionally substituted benzimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzothiadiazolyl, an optionally substituted benzoxadiazolyl, an optionally substituted indolyl, an optionally substituted tetrahydroindolyl, an optionally substituted azaindolyl, an optionally substituted indazolyl, an optionally substituted imidazopyridyl, an optionally substituted quinazolinyl, an optionally substituted purinyl, an optionally substituted pyrrolo[2,3]pyrimidinyl, an optionally substituted pyrazolo[3,4]pyrimidinyl, or an optionally substituted benzo(b)thienyl.

In a preferred embodiment, R' and L' are absent and R" is

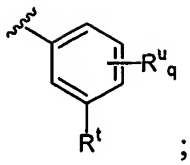


;

wherein: L is NR^i, O, or S; L' is N or CR^i; R^t is H, halogen, CN, an optionally substituted alkyl, an optionally substituted cyclyl, an optionally substituted alkyloxy, an optionally substituted alkylcarbonyl, an optionally substituted alkyloxycarbonyl, an optionally substituted aryloxycarbonyl, an optionally substituted heteroaryloxycarbonyl, hydroxyalkyl, an optionally substituted alkylamino, an optionally substituted dialkylamino, aminocarbonyl, or alkylaminocarbonyl; R^u,for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$; R^i is H, alkyl, or alkylcarbonyl;

s is 0, 1, or 2; and q is 0, 1, 2, 3, or 4.

In a preferred embodiment, R' and L' are absent and R" is



;

wherein R^t is H, halogen, CN, alkyl, cyclyl, alkyloxy, alkylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, alkylamino, aminocarbonyl, or alkylaminocarbonyl; R^u, for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$; and q is 0, 1, 2, 3, or 4.

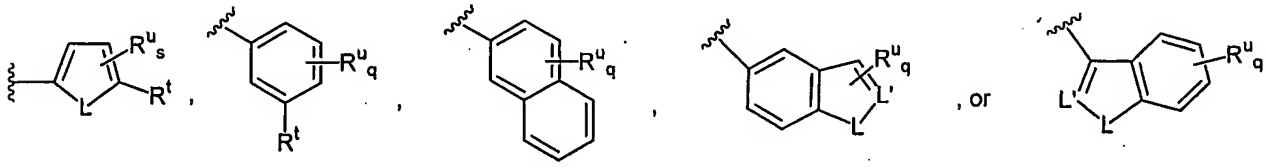
A is O or NR^k. In a preferred embodiment, A is NR^k; and R^k is H, methyl, ethyl, or acetyl, preferably, R^k is H.

In a further embodiment, Z is N and W is O.

Y is absent, O, S, NH, $N(CH_3)$, or CH_2, and n is 0, 1, 2, 3, or 4. Preferably, Y is O and n is 2.

In a further embodiment, R_3 is an optionally substituted aryl or an optionally substituted heteroaryl. Preferably, R_3 is pyridinyl, 1-oxy-pyridinyl, 1*H*-pyridin-2-one, moropholin-4-yl, 4-methyl-piperazin-1-yl, or 2-oxo-oxazolidin-3-yl.

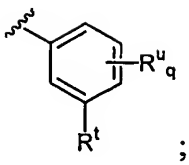
In another embodiment, R' and L' are absent and R" is



;

wherein: L is NR^i, O, or S; L' is N or CR^i; R^t is H, halogen, CN, an optionally substituted alkyl, an optionally substituted cyclyl, an optionally substituted alkyloxy, an optionally substituted alkylcarbonyl, an optionally substituted alkyloxycarbonyl, an optionally substituted aryloxycarbonyl, an optionally substituted heteroaryloxycarbonyl, hydroxyalkyl, an optionally substituted alkylamino, an optionally substituted dialkylamino, aminocarbonyl, or alkylaminocarbonyl; R^u,for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$; R^i is H, alkyl, or alkylcarbonyl; s is 0, 1, or 2; and q is 0, 1, 2, 3, or 4.

In another embodiment, R' and L' are absent and R" is



wherein R^t is H, halogen, CN, alkyl, cyclyl, alkyloxy, alkylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, alkylamino, aminocarbonyl, or alkylaminocarbonyl; R^u, for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$; and q is 0, 1, 2, 3, or 4. Preferably, R^t is CH_3, Cl, or OCH_3. Preferably, R^u is H or CH_3 and q is 1.

In another embodiment, each of of Q, U and V is, independently, N or CH, provided that at least one of Q, U, and V is N. Preferably, two of Q, U and V are N, and the other is CH; Q and U each are N and V is CH; U and V are N, and Q is CH; Q and V are N and Q is CH.

Set forth below are exemplary compounds of this invention:

Compound **1**: *N*-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-*N'*-*m*-tolyl-hydrazine;

Compound **2**: *N*-(3-Chloro-phenyl)- *N'*-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine;

Compound **3**: *N*-(3-Methoxy-phenyl)- *N'*-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine;

Compound **4**: *N*-(2,5-Dimethyl-phenyl)- *N'*-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine;

Compound **5**: 1-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

Compound **6**: N-[2-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **7**: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **8**: N-[6-Morpholin-4-yl-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **9**: 3-{2-[4-Morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-2-yloxy]-ethyl}-oxazolidin-2-one;

Compound **10**: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **11**: 3-{2-[4-Morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyridin-2-yloxy]-ethyl}-oxazolidin-2-one;

Compound **12**: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **13**: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **14**: 3-{2-[4-Morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-ethyl}-oxazolidin-2-one;

Compound **15**: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **16**: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-m-tolyl-hydrazine;

Compound **17**: 3-{2-[6-Morpholin-4-yl-2-(m-tolyl-hydrazonomethyl)-pyrimidin-4-yloxy]-ethyl}-oxazolidin-2-one;

Compound **18**: Methyl-{2-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-2-yloxy]-ethyl}-amine;

Compound **19**: Methyl-{2-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyridin-2-yloxy]-ethyl}-amine;

Compound **20**: 2-Methyl-1-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-2-yloxy]-propan-2-ol;

Compound **21**: 2-Methyl-1-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyridin-2-yloxy]-propan-2-ol;

Compound **22**: 2-Methyl-1-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-2-yloxy]-propan-2-ol;

Compound **23**: 2-Methyl-1-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyridin-2-yloxy]-propan-2-ol;

Compound **24**: Methyl-{2-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-ethyl}-amine;

Compound **25**: Methyl-{2-[6-morpholin-4-yl-2-(m-tolyl-hydrazonomethyl)-pyrimidin-4-yloxy]-ethyl}-amine;

Compound **26**: 2-Methyl-1-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-propan-2-ol;

Compound **27**: 2-Methyl-1-[2-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-4-yloxy]-propan-2-ol;

Compound **28**: -Methyl-1-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-propan-2-ol;

Compound **29**: 2-Methyl-1-[2-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-4-yloxy]-propan-2-ol;

Compound **30**: N-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **31**: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **32**: N-[6-Morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **33**: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **34**: Methyl-{2-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-2-yloxy]-ethyl}-amine;

Compound **35**: Methyl-{2-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyridin-2-yloxy]-ethyl}-amine;

Compound **36**: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **37**: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **38**: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **39**: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

Compound **40**: Methyl-{2-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-ethyl}-amine;

Compound **41**: Methyl-{2-[2-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-4-yloxy]-ethyl}-amine;

Compound **42**: N-(1H-Indol-3-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **43**: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **44**: N-(1H-Indol-3-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **45**: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **46**: (2-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

Compound **47**: (2-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

Compound **48**: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **49**: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **50**: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **51**: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **52**: (2-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

Compound **53**: (2-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

Compound **54**: 1-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

Compound **55**: 1-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

Compound **56**: 1-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

Compound **57**: 1-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

Compound **58**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **59**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **60**: 1-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

Compound **61**: 1-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

Compound **62**: 1-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

Compound **63**: 1-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

Compound **64**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **65**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **66**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **67**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **68**: (2-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

Compound **69**: (2-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

Compound **70**: 3-{N'-[2-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

Compound **71**: 3-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-benzamide;

Compound **72**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **73**: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **74**: (2-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

Compound **75**: (2-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

Compound **76**: 3-{N'-[4-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

Compound **77**: 3-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

Compound **78**: 3-{N'-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

Compound **79**: 3-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-benzamide;

Compound **80**: 3-{N'-[6-Morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

Compound **81**: 3-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-benzamide;

Compound **82**: 3-{N'-[2-(2-Methylamino-ethoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

Compound **83**: 3-{N'-[6-(2-Methylamino-ethoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-benzamide;

Compound **84**: 3-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

Compound **85**: 3-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-benzamide;

Compound **86**: 3-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

Compound **87**: 3-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-benzamide;

Compound **88**: 3-{N'-[4-(2-Methylamino-ethoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

Compound **89**: 3-{N'-[6-(2-Methylamino-ethoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

Compound **90**: 4-Methyl-2-{N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

Compound **91**: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **92**: 4-Methyl-2-{N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

Compound **93**: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **94**: 4-Methyl-2-{N'-[2-(2-methylamino-ethoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

Compound **95**: 4-Methyl-2-{N'-[6-(2-methylamino-ethoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **96**: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **97**: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **98**: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **99**: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **100**: 4-Methyl-2-{N'-[4-(2-methylamino-ethoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenylamine;

Compound **101**: 4-Methyl-2-{N'-[6-(2-methylamino-ethoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

Compound **102**: 1-{4-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

Compound **103**: 1-{6-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

Compound **104**: N-(5-Ethyl-thiophen-2-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **105**: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **106**: N-(5-Ethyl-thiophen-2-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **107**: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **108**: 1-{4-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

Compound **109**: 1-{6-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

Compound **110**: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **111**: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **112**: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **113**: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **114**: (2-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

Compound **115**: (2-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

Compound **116**: 1-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

Compound **117**: 1-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

Compound **118**: N-(4,5-Dimethyl-furan-2-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **119**: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **120**: (2-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

Compound **121**: (2-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

Compound **122**: 1-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

Compound **123**: 1-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

Compound **124**: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **125**: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **126**: N-(4,5-Dimethyl-furan-2-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **127**: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **128**: (2-{4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

Compound **129**: (2-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

Compound **130**: 1-{4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

Compound **131**: 1-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

Compound **132**: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **133**: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **134**: (2-{4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

Compound **135**: (2-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

Compound **136**: {4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

Compound **137**: 1-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

Compound **138**: 4-{N'-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

Compound **139**: 4-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenol;

Compound **140**: 4-{N'-[6-Morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

Compound **141**: 4-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenol;

Compound **142**: 4-{N'-[2-(2-Methylamino-ethoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

Compound **143**: 4-{N'-[6-(2-Methylamino-ethoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-phenol;

Compound **144**: 4-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

Compound **145**: 4-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenol;

Compound **146**: 4-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

Compound **147**: 4-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenol;

Compound **148**: 4-{N'-[4-(2-Methylamino-ethoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

Compound **149**: 4-{N'-[6-(2-Methylamino-ethoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

Compound **150**: 4-{N'-[2-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

Compound **151**: 4-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-phenol;

Compound **152**: N-(3,4-Dimethyl-phenyl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **153**: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **154**: N-(3,4-Dimethyl-phenyl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

Compound **155**: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

Compound **156**: 4-{N'-[4-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

Compound **157**: 4-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

Compound **158**: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **159**: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **160**: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

Compound **161**: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

Compound **162**: (2-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

Compound **163**: (2-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

Compound **164**: 1-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

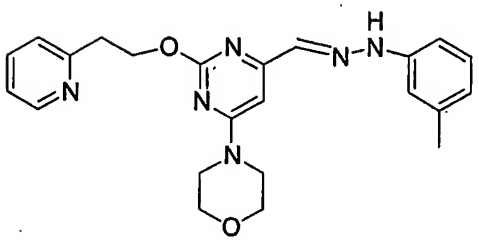
Compound **165**: 1-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

Compound **166**: (2-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

Compound **167**: (2-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

Compound **168**: 1-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol.

Their structures are delineated below.



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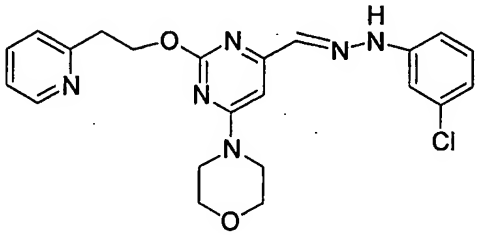

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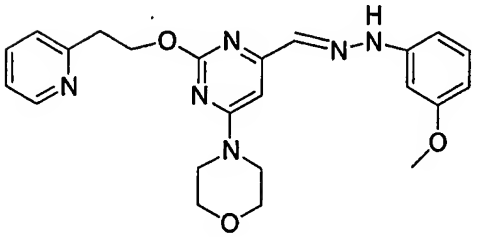

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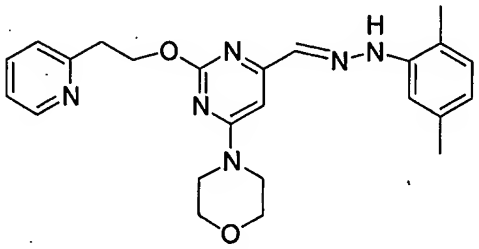

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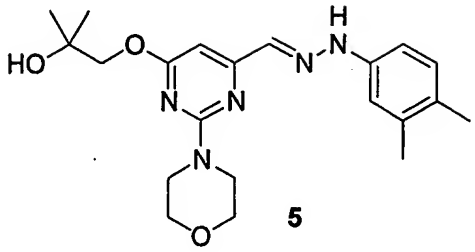

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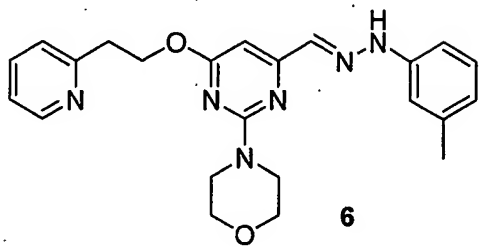

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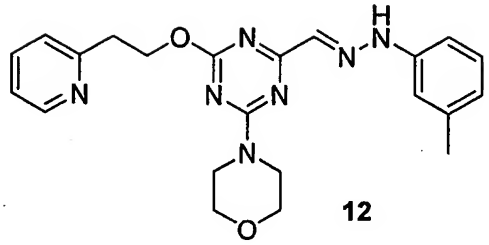

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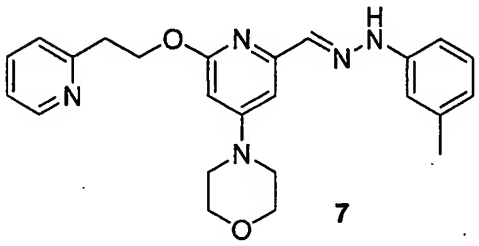

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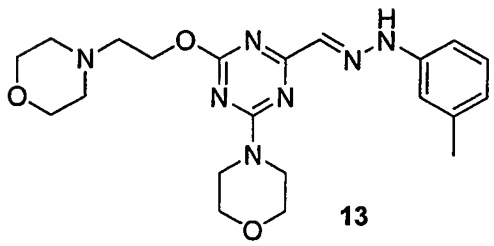

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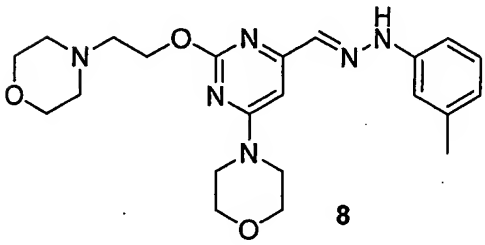

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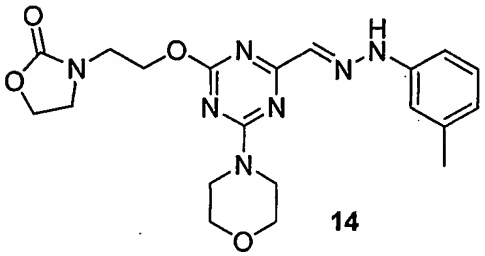

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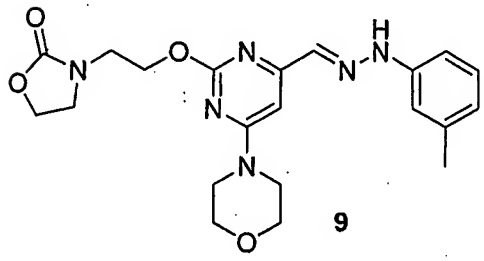

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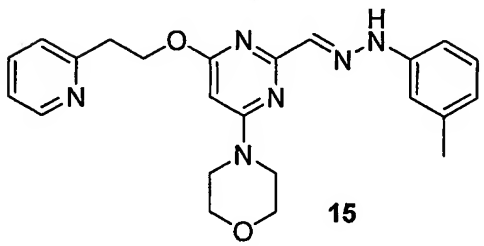

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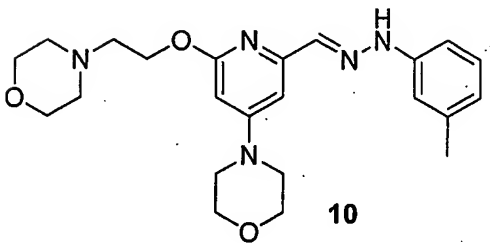

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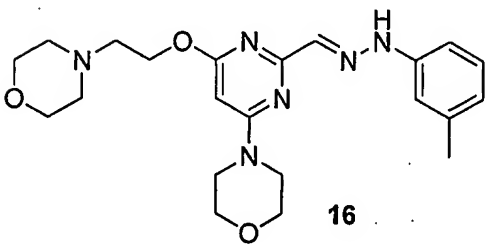

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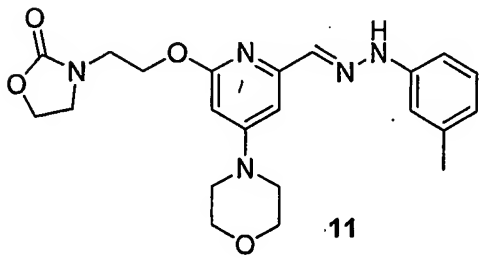

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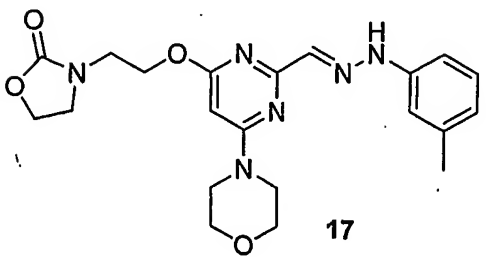

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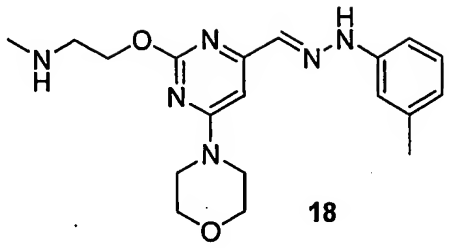

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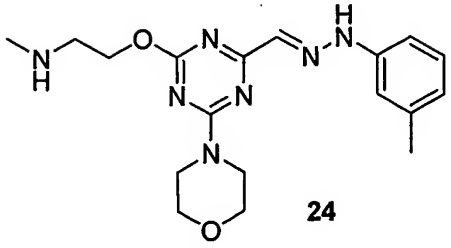

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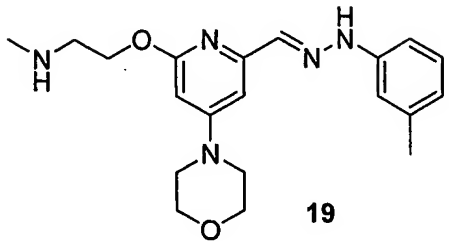

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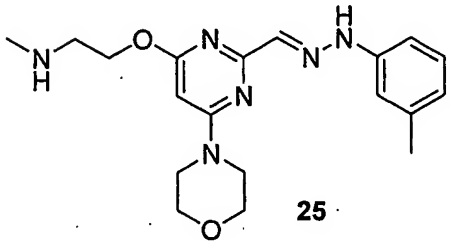

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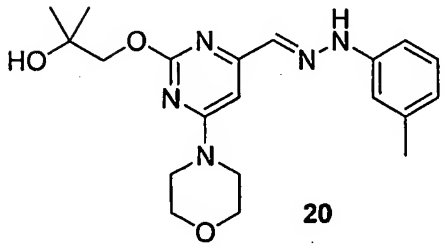

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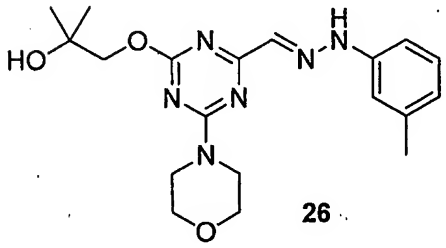

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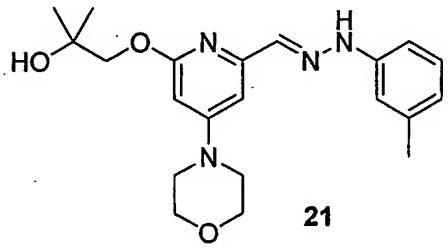

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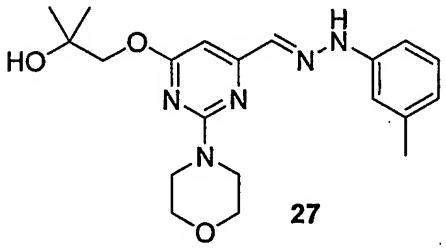

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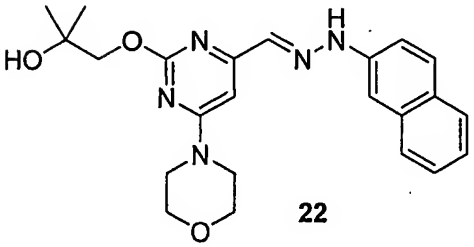

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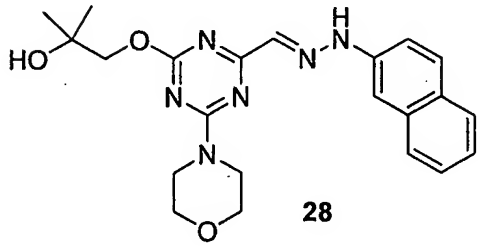

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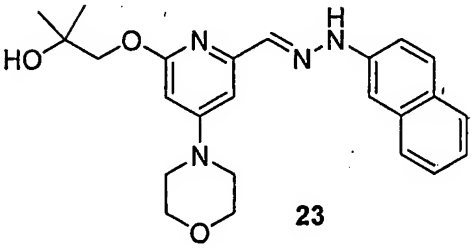

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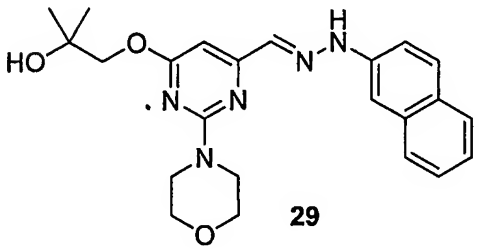

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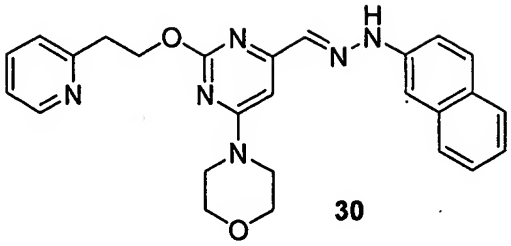

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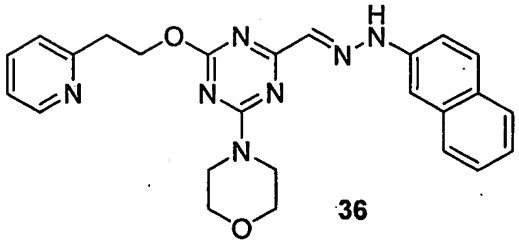

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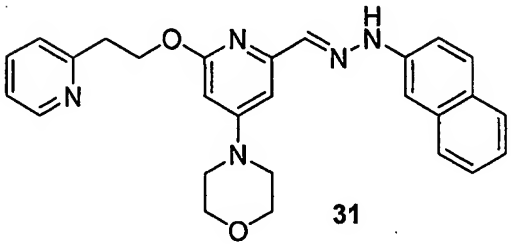

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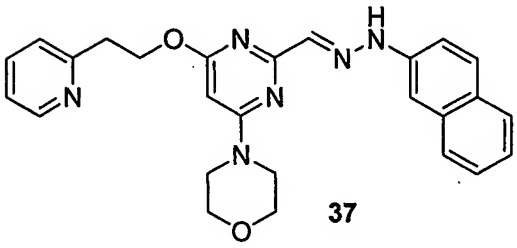

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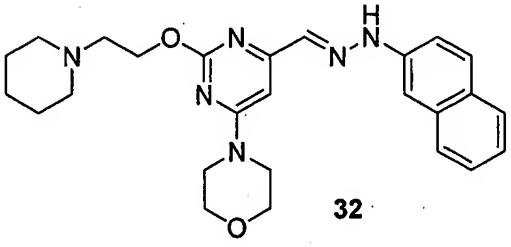

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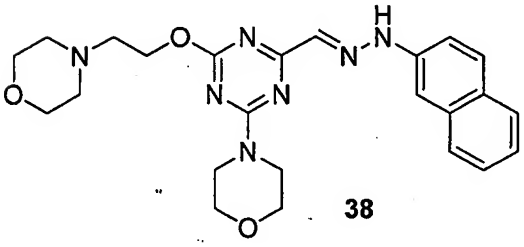

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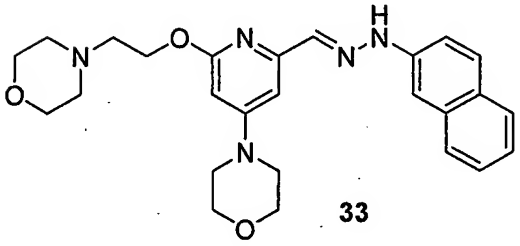

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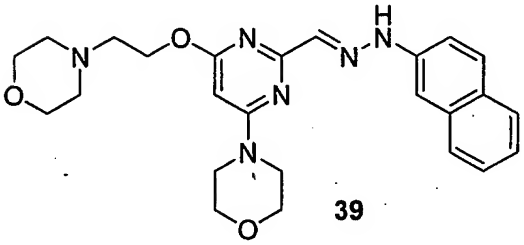

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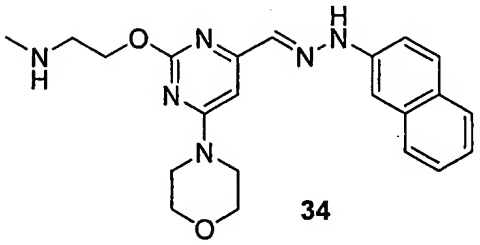

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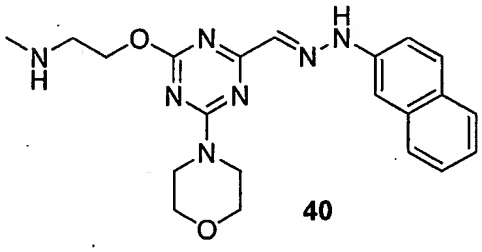

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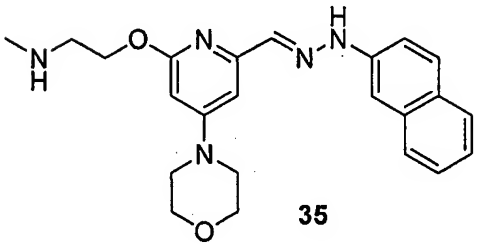

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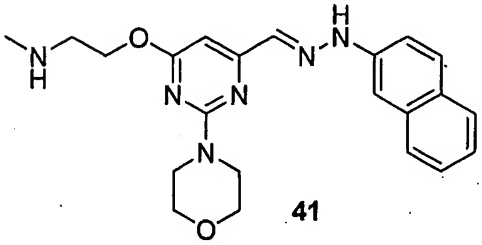

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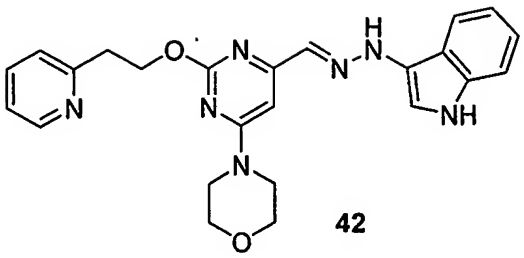

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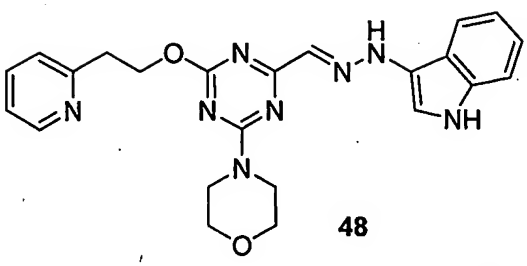

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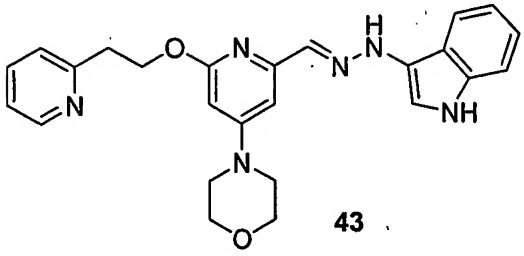

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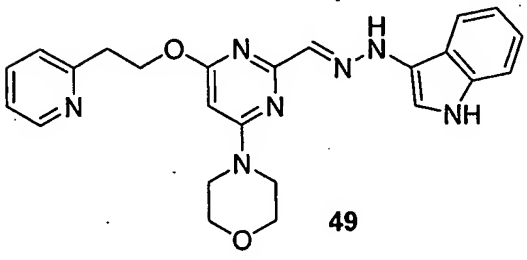

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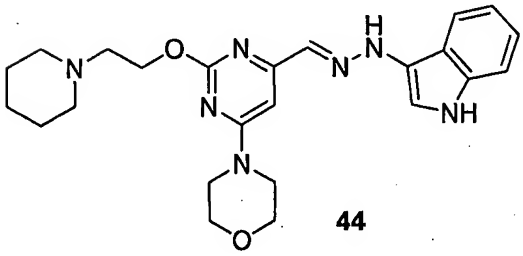

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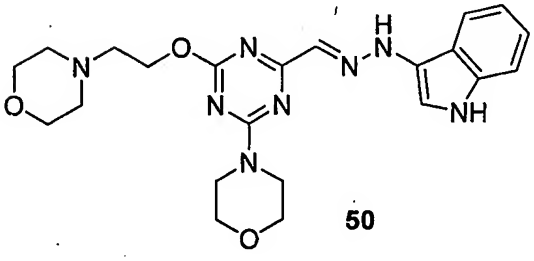

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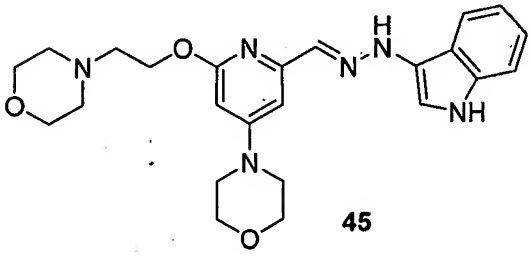

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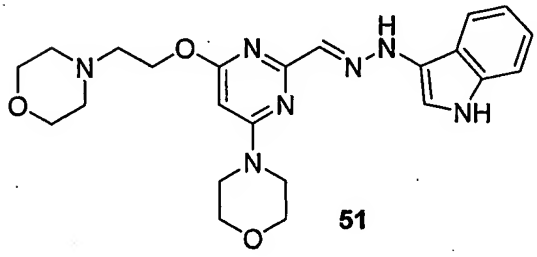

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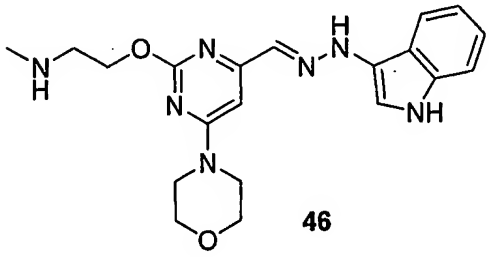

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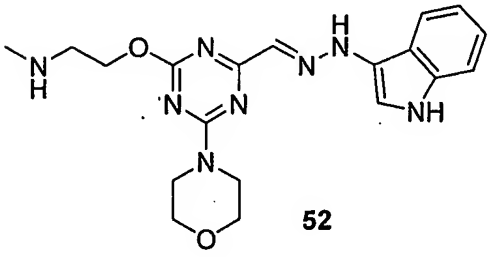

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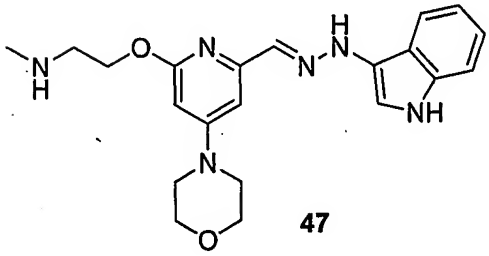

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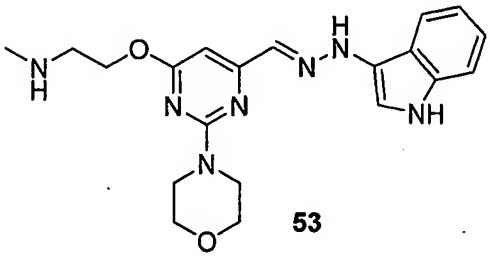

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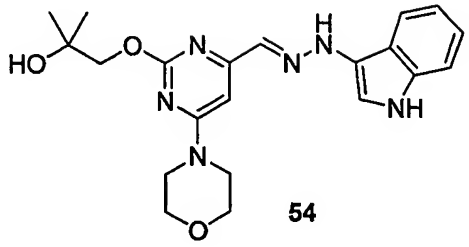

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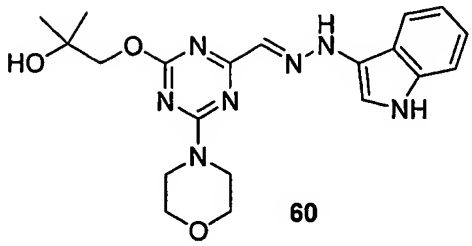

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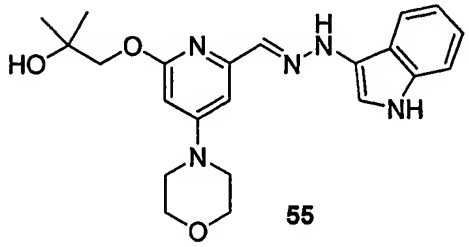

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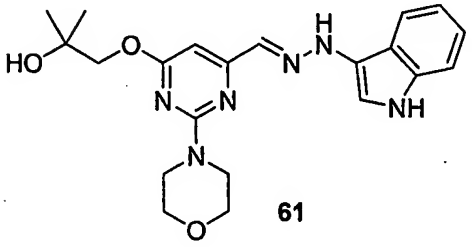

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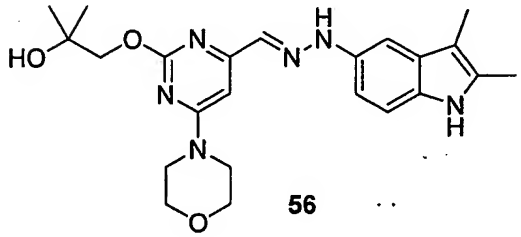

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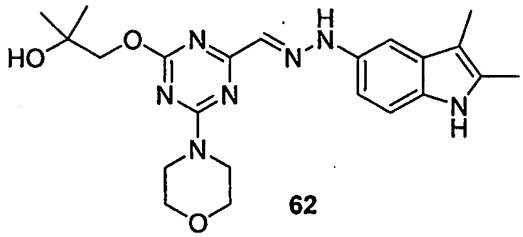

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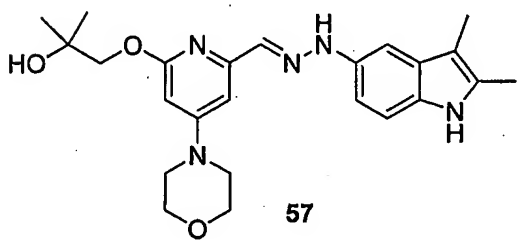

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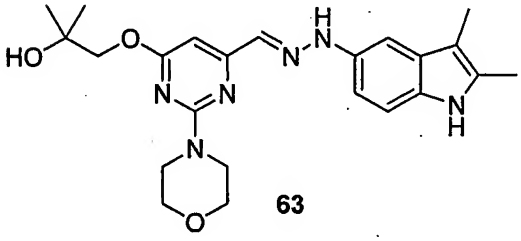

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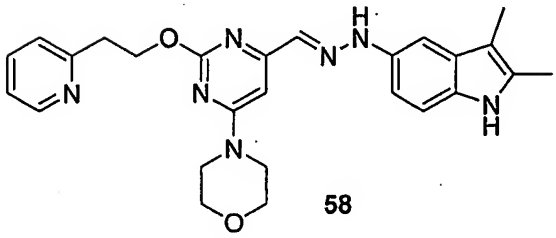

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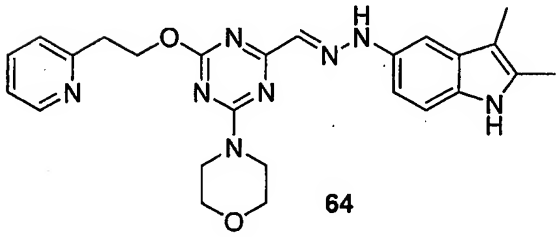

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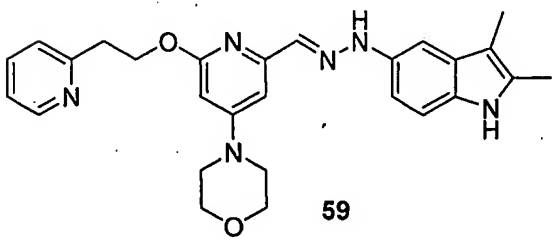

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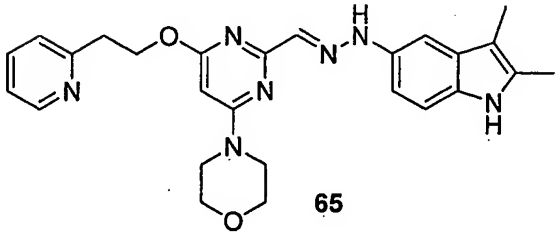

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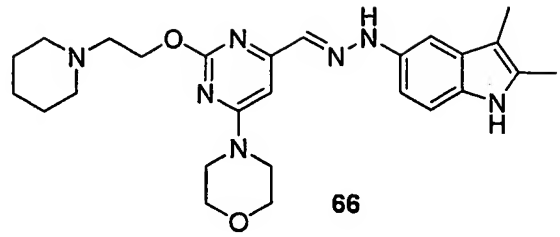

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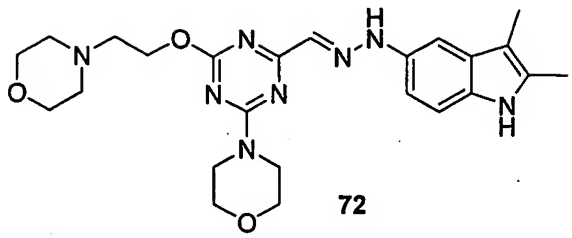

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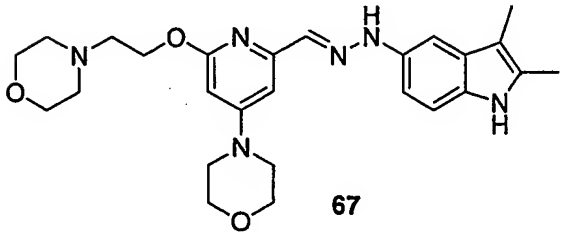

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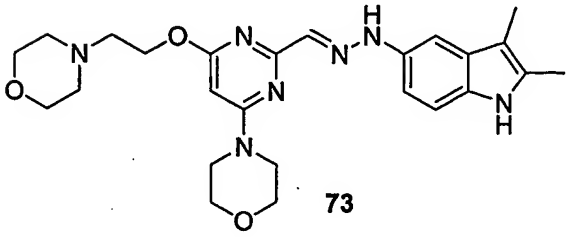

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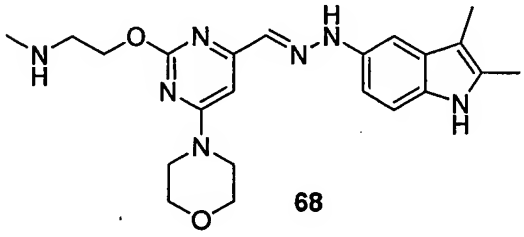

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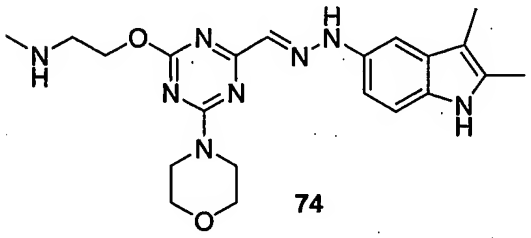

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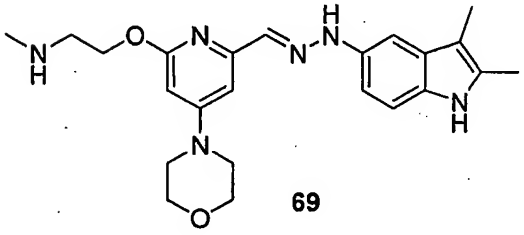

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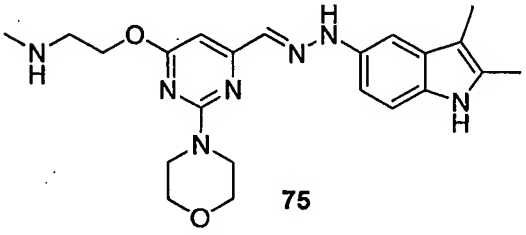

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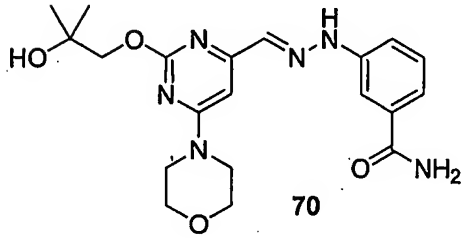

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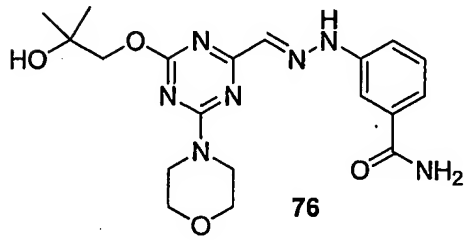

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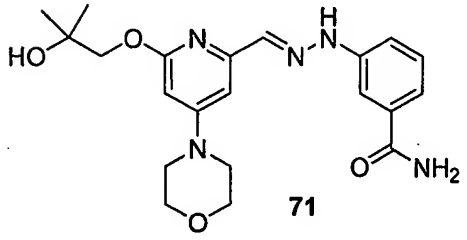

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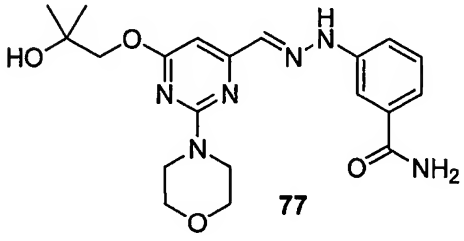

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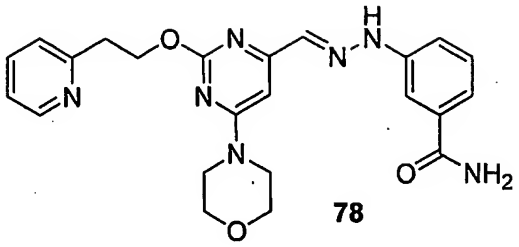

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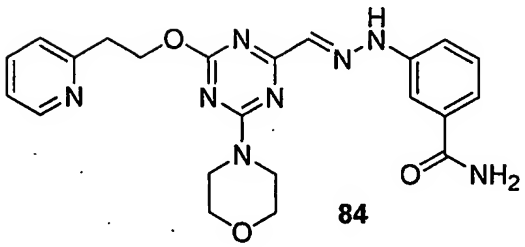

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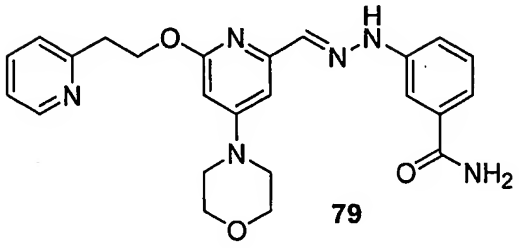

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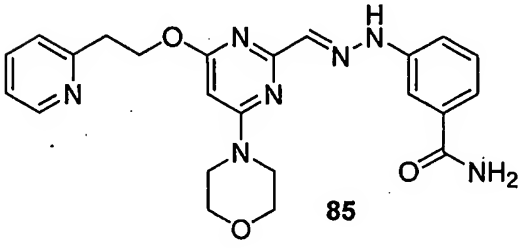

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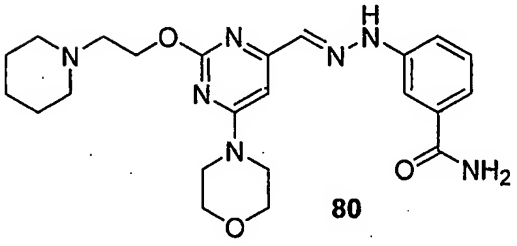

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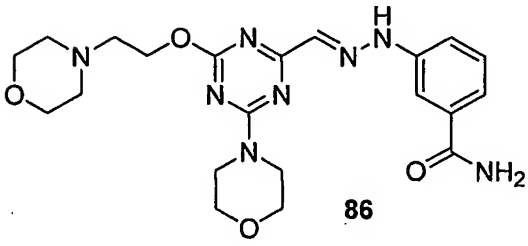

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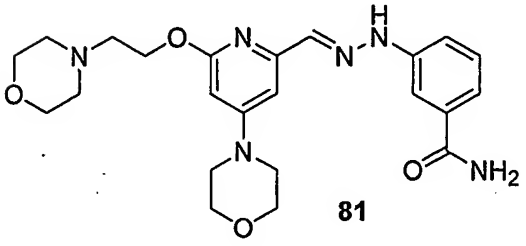

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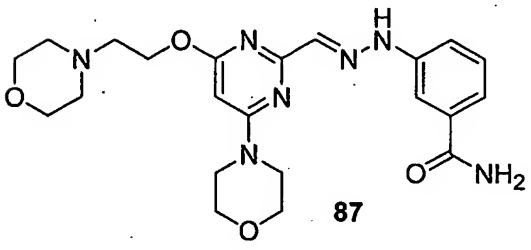

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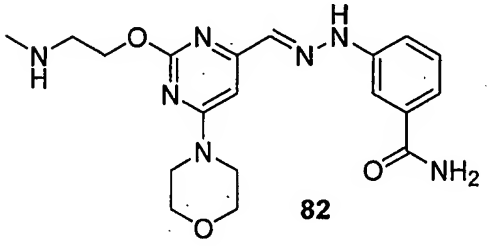

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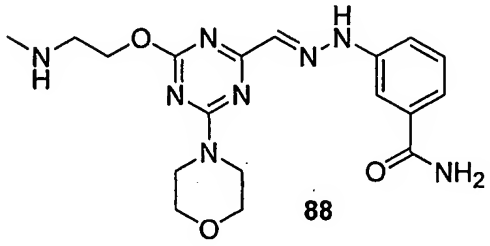

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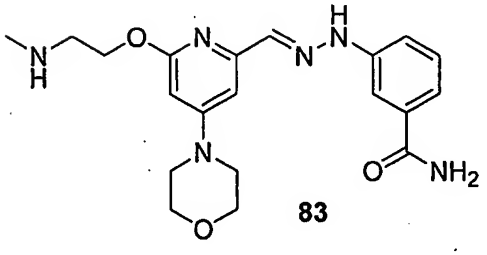

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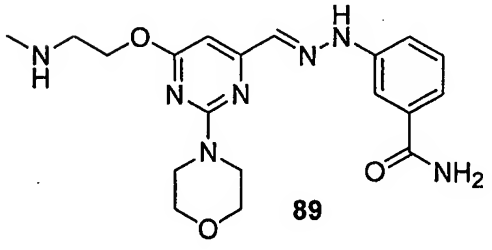

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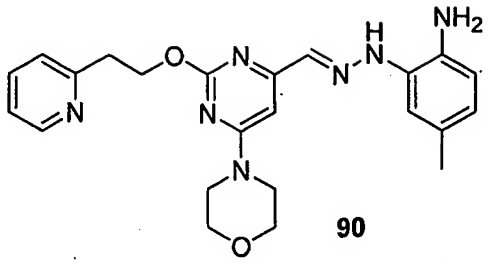

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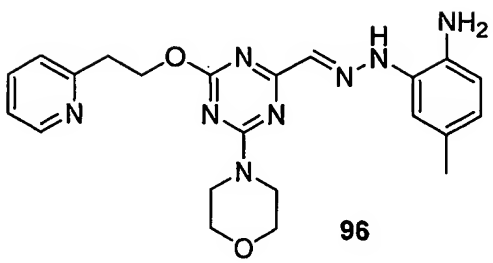

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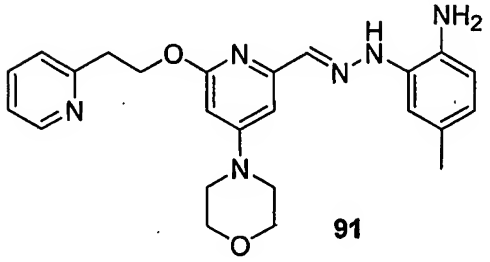

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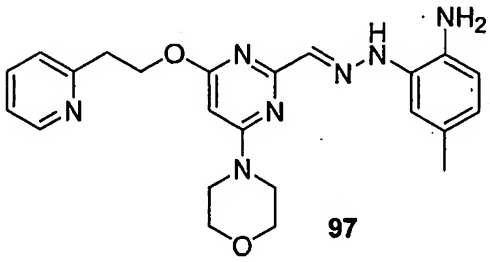

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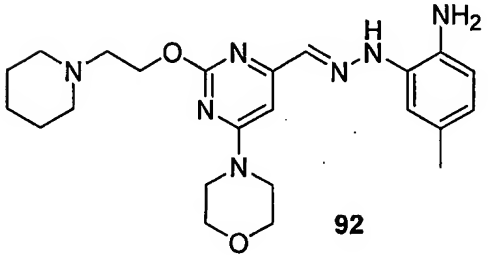

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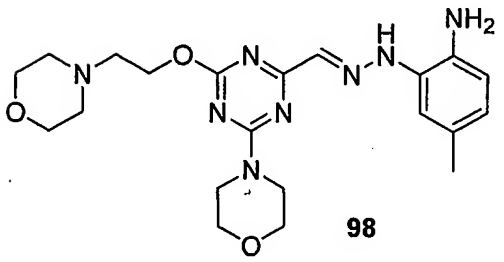

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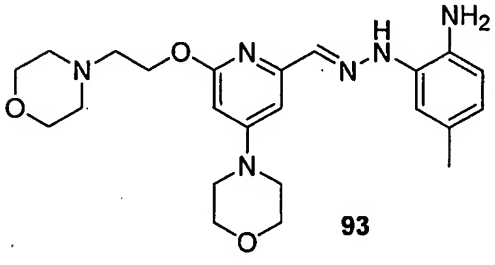

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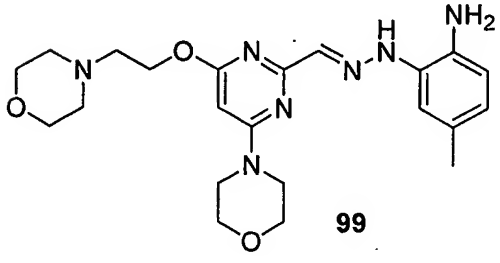

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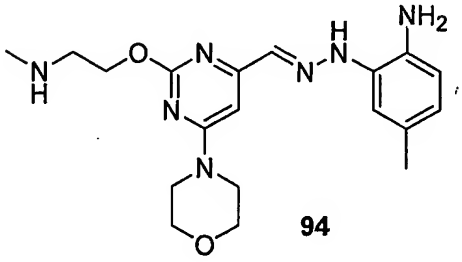

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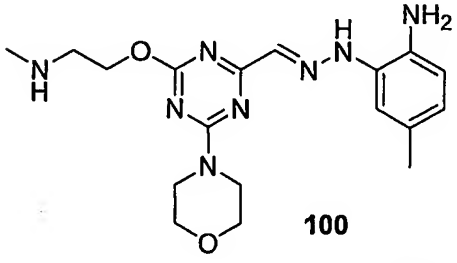

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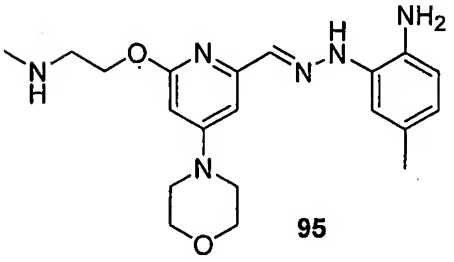

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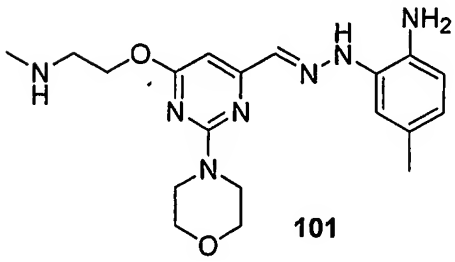

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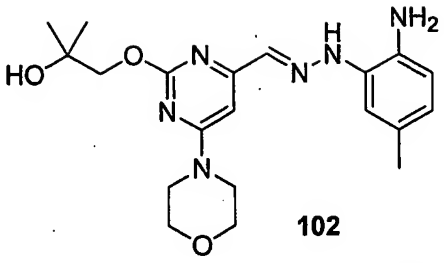

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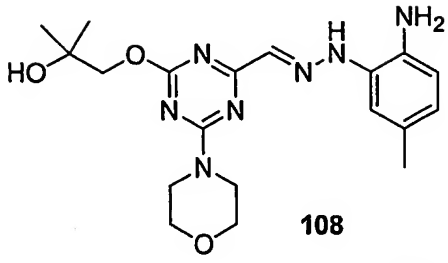

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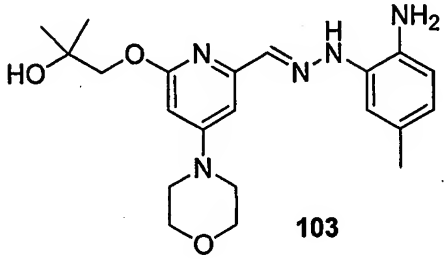

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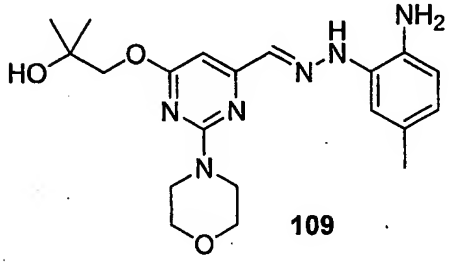

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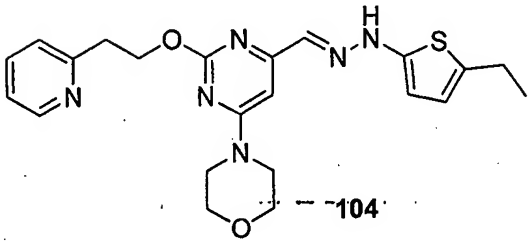

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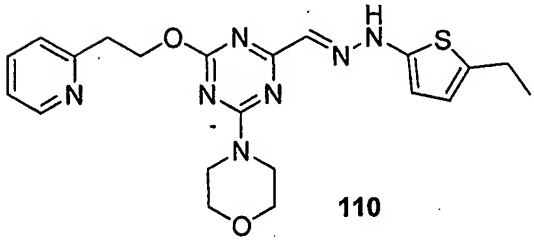

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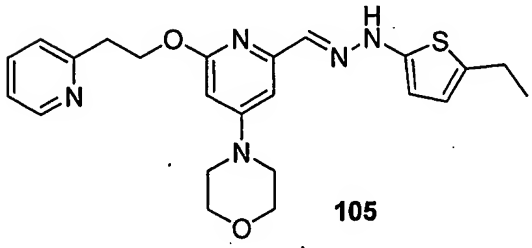

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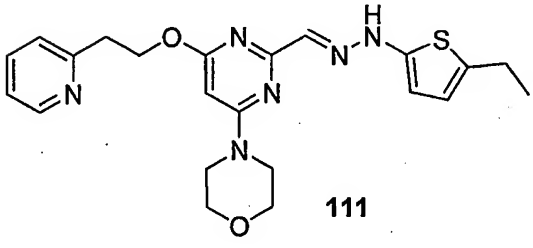

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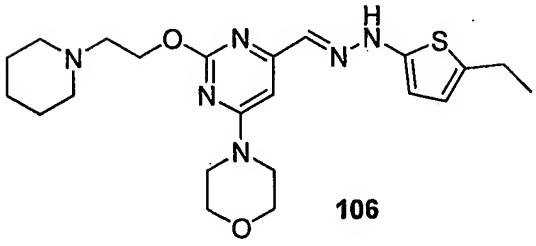

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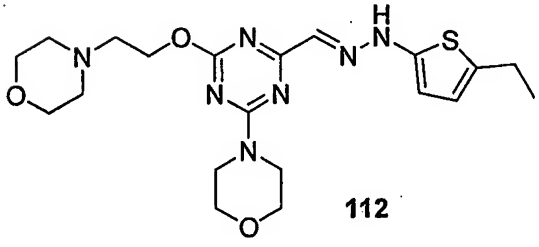

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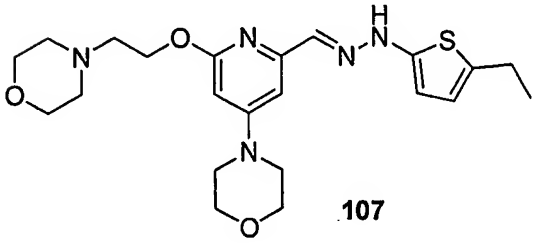

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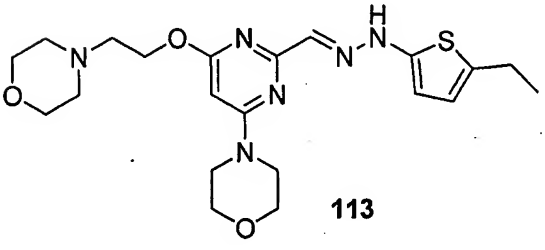

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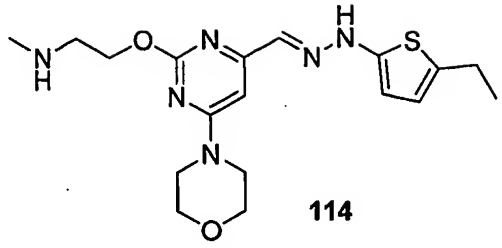

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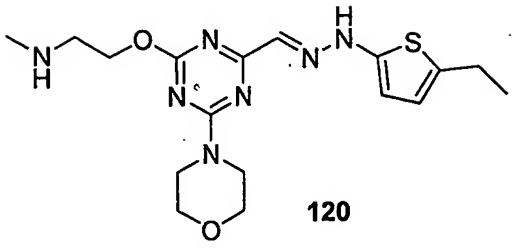

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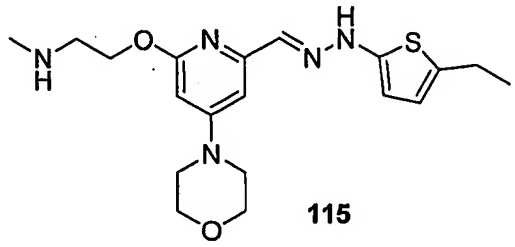

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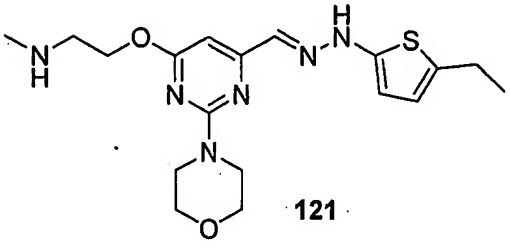

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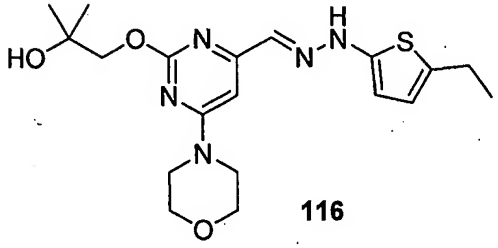

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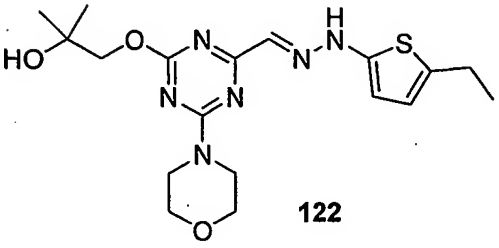

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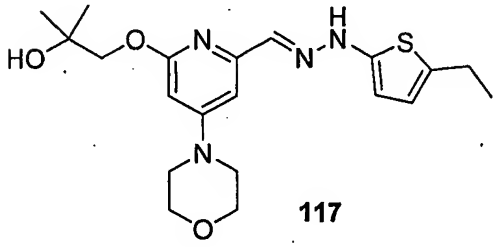

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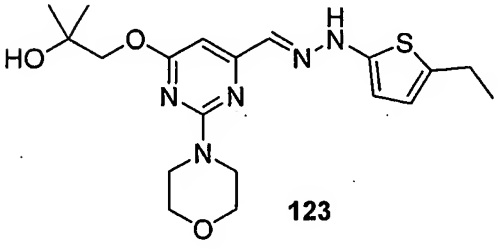

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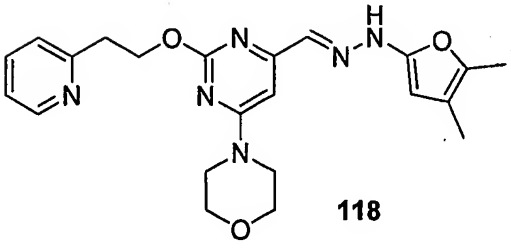

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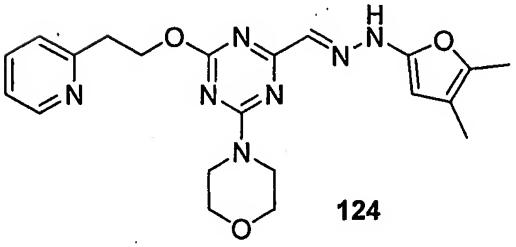

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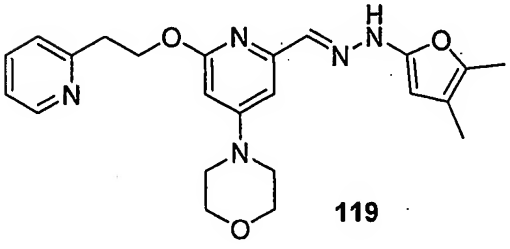

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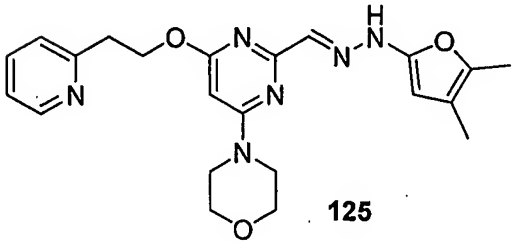

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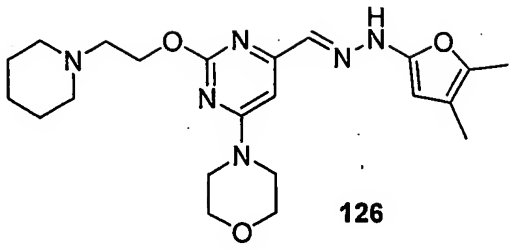

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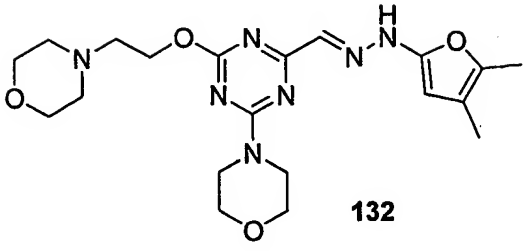

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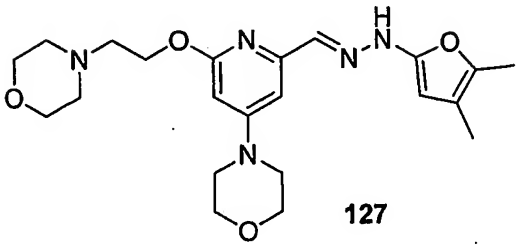

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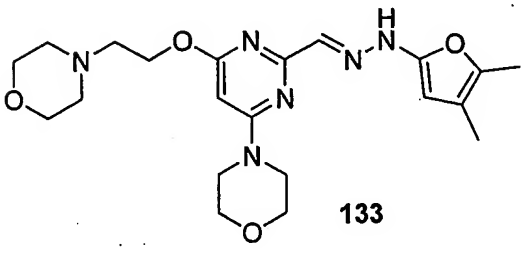

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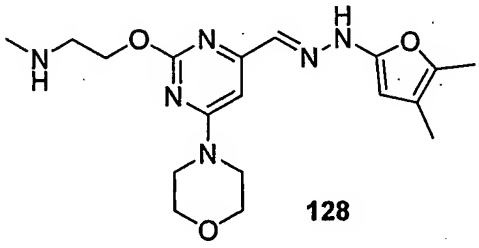

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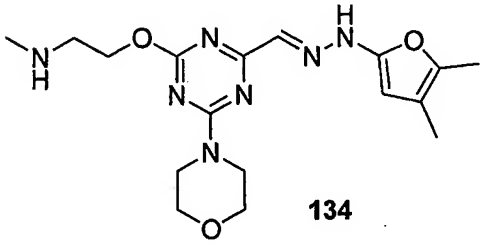

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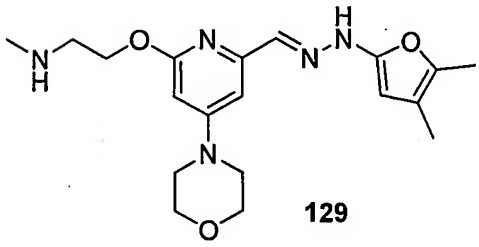

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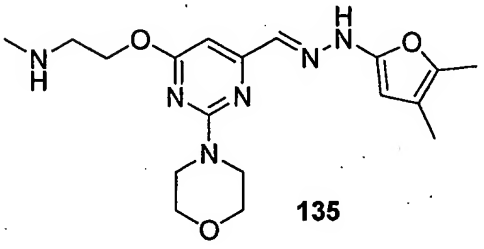

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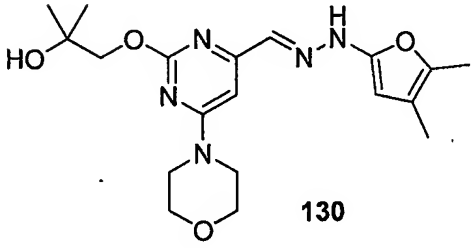

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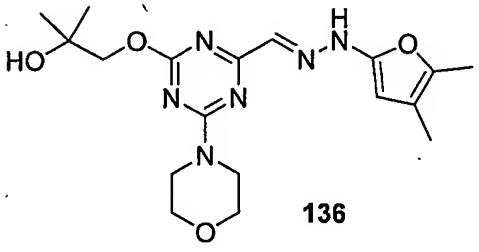

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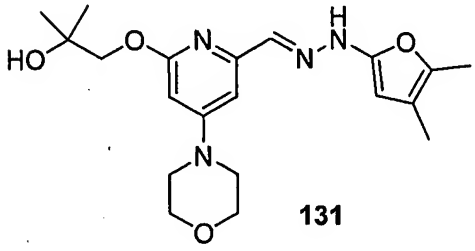

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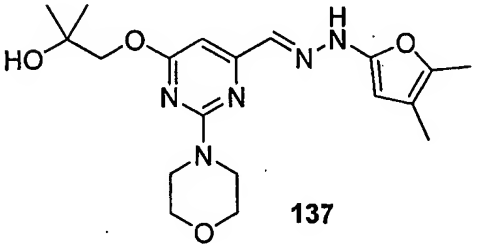

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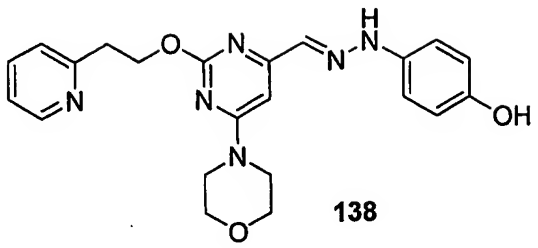

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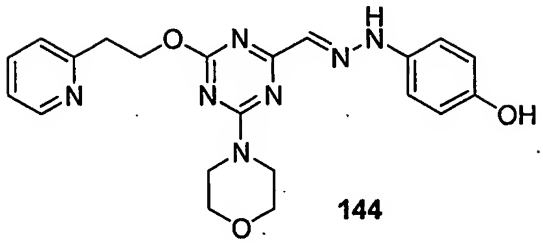

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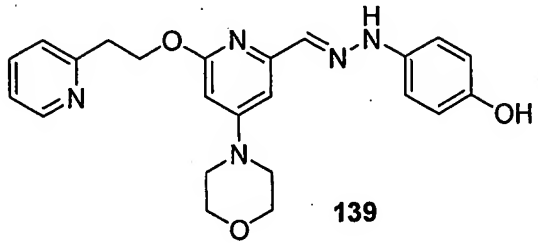

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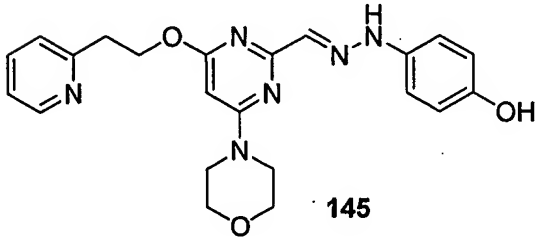

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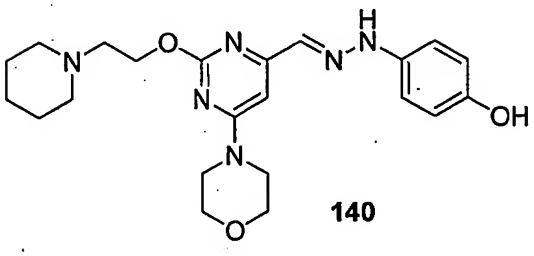

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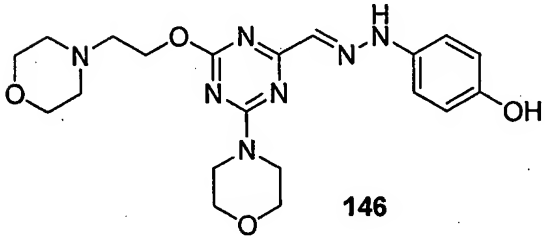

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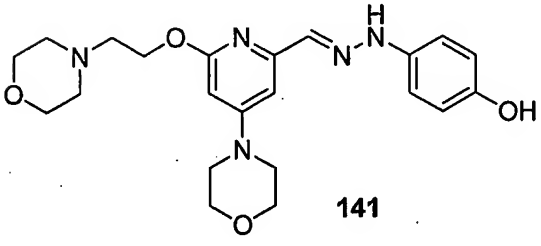

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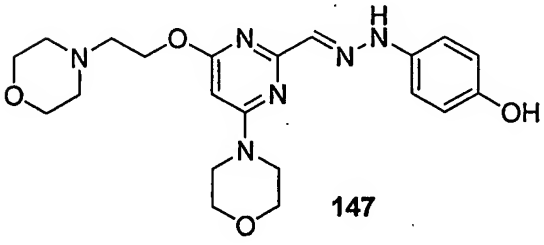

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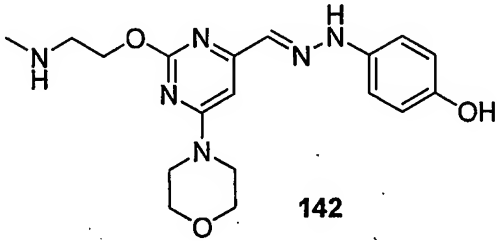

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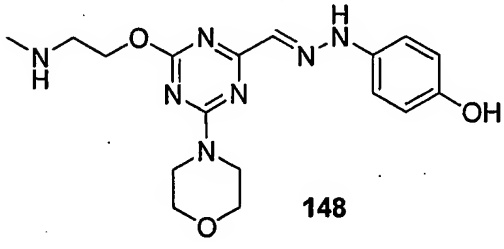

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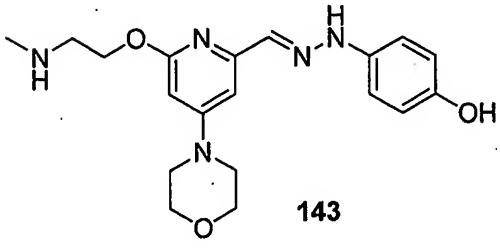

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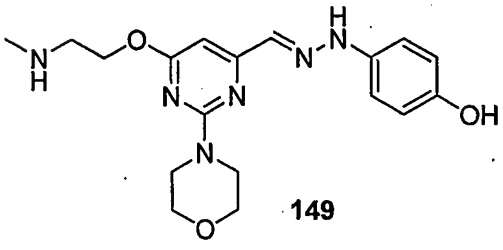

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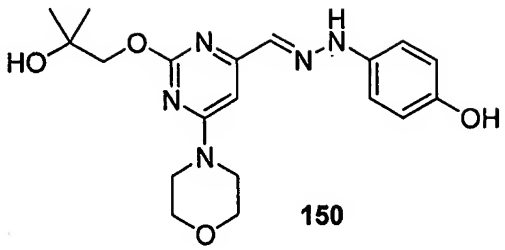

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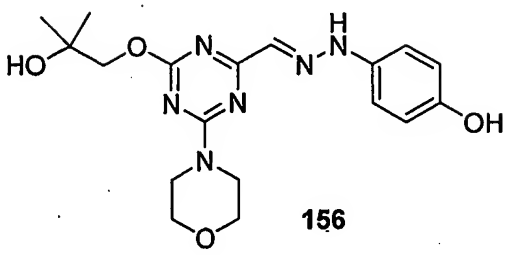

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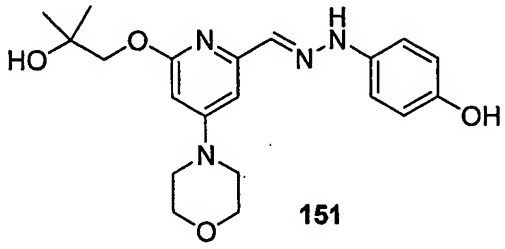

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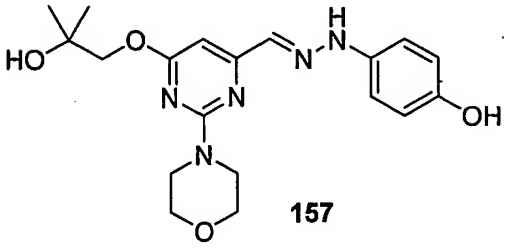

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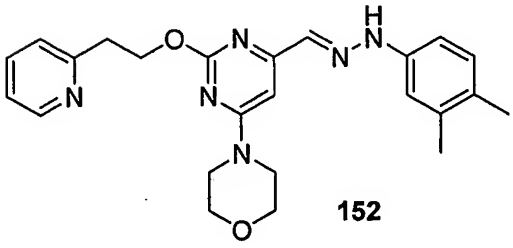

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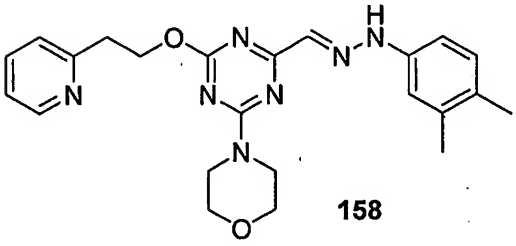

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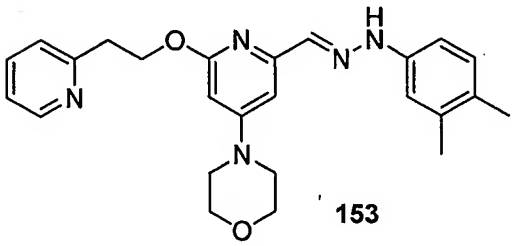

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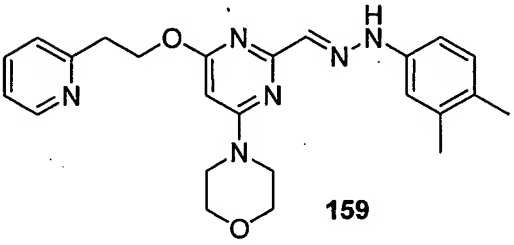

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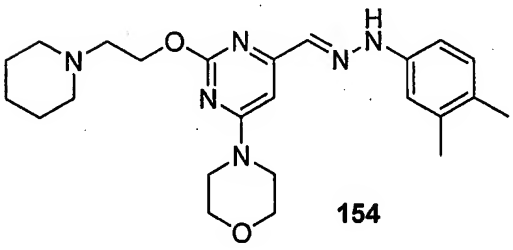

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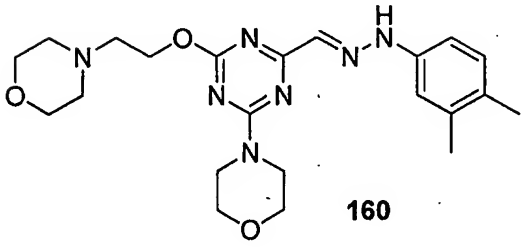

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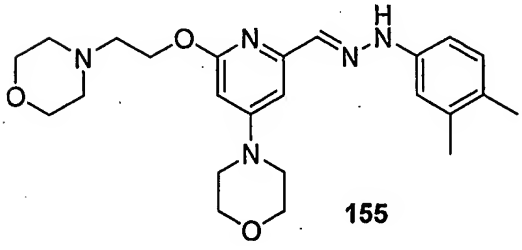

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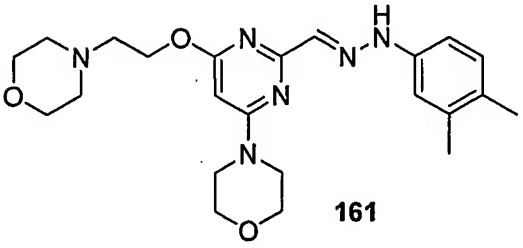

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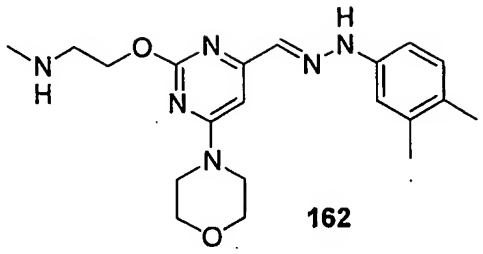

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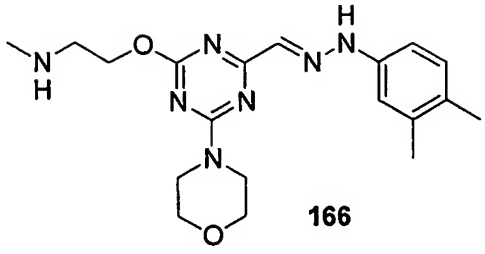

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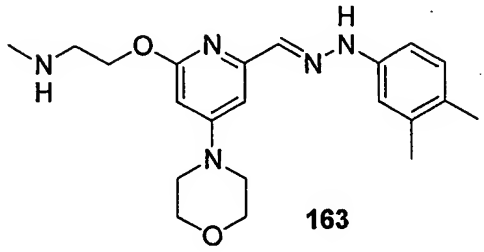

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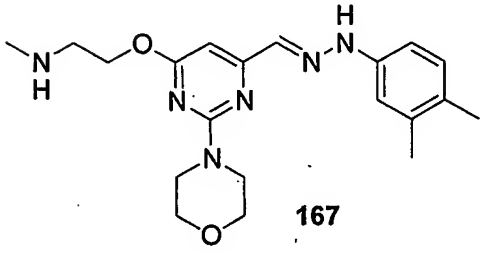

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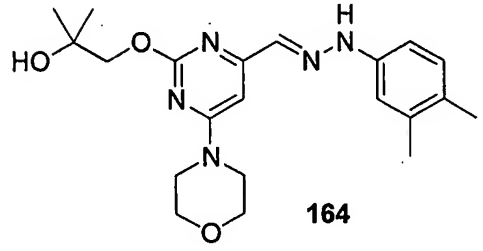

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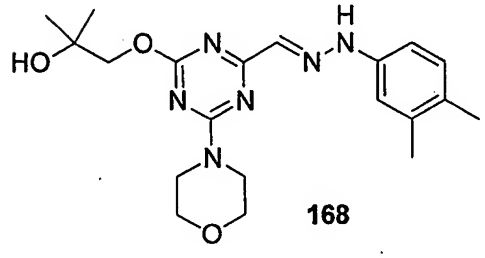

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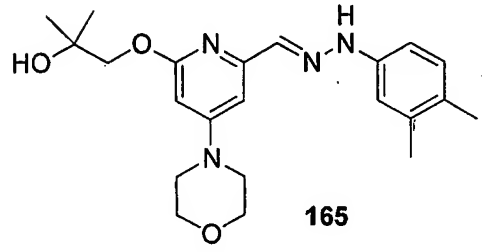

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In one aspect, the invention comprises a pharmaceutical composition comprising a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof, and a pharmaceutically acceptable carrier.

The compounds of the invention are particularly useful in inhibiting the production of IL-12 and/or inhibiting the production of cytokines such as IL-23 and IL-27 which stimulate and/or otherwise augment the production of IL-12 and/or the proliferation of T_H1 lymphocytes. Thus, in one aspect, the present invention provides a method of inhibiting the production of IL-12 and/or inhibiting the production of a cytokine that stimulates or augments the production of IL-12 (e.g., IL-23 and IL-27) in a subject by administering to the subject an effective amount of a compound of any of the formulae herein, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

Since one of the function of IL-12 is induction of INF-γ expression from T and NK cells which promotes the development of T_H1 T lymphocyte type, the compounds of the invention can be used to inhibit the production of T_H1 cells. Therefore, in another aspect, the invention features a method of inhibiting the proliferation and/or development/proliferation of T_H1 cells in a subject by administering to the subject an effective amount of a compound of any of the formulae herein, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

In another aspect, the invention provides a method of treating an IL-12 overproduction-related disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the formulae herein or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof. IL-12 overproduction disorders include, but are not limited to multiple sclerosis, sepsis, myasthenia gravis, autoimmune neuropathies, Guillain-Barré syndrome, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, psoriatic arthritis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, ulcerative colitis, interstitial pulmonary fibrosis, myelofibrosis, hepatic fibrosis, myocarditis, thyroditis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland; rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, spondyloarthropathies, ankylosing spondylitis, Sjogren's syndrome and graft-versus-host disease.

Although the mechanism is not yet understood, compounds of the invention have been found to inhibit the formation of osteoclasts (see co-owned PCT Application Number US04/17064, filed on May 28, 2004, the entire teachings of which are incorporated herein by reference). Osteoclasts are unique multinucleated cells within bone that are responsible for bone degradation and resorption. These are the only cells in the body known to be capable of this function. The regulation of osteoclastic formation and activity is only partly understood but it is known that excessive bone resorption by osteoclasts contributes to the pathology of many human diseases associated with excessive bone loss. Thus, in one aspect, the invention provides a method of treating or preventing disorders associated with excessive bone loss, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate,

clathrate, hydrate, polymorph, or prodrug thereof. Disorders associated with excessive bone loss include, but are not limited to periodontal disease, non-malignant bone disorders, osteoporosis, Paget's disease of bone, osteogenesis imperfecta, fibrous dysplasia, and primary hyperparathyroidism, estrogen deficiency, inflammatory bone loss, bone malignancy, arthritis, osteopetrosis, hypercalcemia of malignancy (HCM), osteolytic bone lesions of multiple myeloma and osteolytic bone metastases of breast cancer, and metastatic cancers.

In another aspect, the invention provides a method for inhibiting osteoclast formation *in vitro* or *in vivo*, comprising contacting a pre-osteoclast cell with an effective amount of a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

In another aspect, the invention provides a method of treating or preventing a disorder associated with excessive bone resorption by osteoclasts in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any of the formulae herein or pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof.

The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

Other embodiments include the compounds, intermediates, or a pharmaceutically acceptable salt, solvate, clatharate, hydrate, polymorph, or prodrug thereof delineated herein, or compositions including them; as well as their methods of use for treatment or prevention of disease, inhibition of IL-12, or modulation of IL-12 mediated disease.

Another embodiment is a method of making a compound of any of the formulae herein using any one, or combination of, reactions delineated herein. The method can include the use of one or more intermediates or chemical reagents delineated herein.

Another aspect is a radiolabeled compound of any of the formulae delineated herein. Such compounds have one or more radioactive atoms (e.g., ^{3}H, ^{2}H, ^{14}C, ^{13}C, ^{35}S, ^{32}P, ^{125}I, ^{131}I) introduced into the compound. Such compounds are useful for drug metabolism studies and diagnostics, as well as therapeutic applications.

As used herein, the term "alkyl" refers to a straight-chained or branched hydrocarbon group containing 1 to 12 carbon atoms. The term "lower alkyl" refers to a C1-C6 alkyl chain.

Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, *tert*-butyl, and n-pentyl. Alkyl groups may be optionally substituted with one or more substituents.

The term "alkenyl" refers to an unsaturated hydrocarbon chain that may be a straight chain or branched chain, containing 2 to 12 carbon atoms and at least one carbon-carbon double bond. Alkenyl groups may be optionally substituted with one or more substituents.

The term "alkynyl" refers to an unsaturated hydrocarbon chain that may be a straight chain or branched chain, containing the 2 to 12 carbon atoms and at least one carbon-carbon triple bond. Alkynyl groups may be optionally substituted with one or more substituents.

The sp^2 or sp carbons of an alkenyl group and an alkynyl group, respectively, may optionally be the point of attachment of the alkenyl or alkynyl groups.

The term "alkoxy" refers to an -O-alkyl radical. The term "ester" refers to a -C(O)O-R^k or, where a divalent group is indicated, an "ester" group is –C(O)O- or –OC(O)-. An "amido" is an -C(O)NH_2, and an "N-alkyl-substituted amido" is of the formula C(O)NHR^k; where a divalent "amide" group is indicated, the group is –C(O)N^k- or –N^kC(O)-.

The term "mercapto" refers to a -SH group.

As used herein, the term "halogen" or "halo" means -F, -Cl, -Br or -I.

As used herein, the term "haloalkyl" means an alkyl group in which one or more (including all) of the hydrogen radicals are replaced by a halo group, wherein each halo group is independently selected from –F, -Cl, -Br, and -I. The term "halomethyl" means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include trifluoromethyl, bromomethyl, 1,2-dichloroethyl, 4-iodobutyl, 2-fluoropentyl, and the like.

The term "cycloalkyl" refers to a hydrocarbon 3-8 membered monocyclic or 7-14 membered bicyclic ring system having at least one saturated ring. Cycloalkyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a cycloalkyl group may be substituted by a substituent. Representative examples of cycloalkyl group include cyclopropyl, cyclopentyl, cyclohexyl, cyclobutyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl.

The term "cyclyl" refers to a hydrocarbon 3-8 membered monocyclic or 7-14 membered bicyclic ring system having at least one non-aromatic ring, wherein the non-aromatic ring has some degree of unsaturation. Cyclyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a cyclyl group may be substituted by a substituent. Examples of cyclyl groups include cyclohexenyl, bicyclo[2.2.1]hept-2-enyl, dihydronaphthalenyl, benzocyclopentyl,

cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl,cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclooctatetraenyl, cyclononenyl, cyclononadienyl, cyclodecenyl, cyclodecadienyl and the like.

The term "aryl" refers to a hydrocarbon monocyclic, bicyclic or tricyclic aromatic ring system. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, 4, 5 or 6 atoms of each ring of an aryl group may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, anthracenyl, fluorenyl, indenyl, azulenyl, and the like.

As used herein, the term "aralkyl" means an aryl group that is attached to another group by a $(C_1$-$C_6)$alkylene group. Aralkyl groups may be optionally substituted, either on the aryl portion of the aralkyl group or on the alkylene portion of the aralkyl group, with one or more substituents. Representative aralkyl groups include benzyl, 2-phenyl-ethyl, naphth-3-yl-methyl and the like.

As used herein, the term "alkylene" refers to an alkyl group that has two points of attachment. The term "$(C_1$-$C_6)$alkylene" refers to an alkylene group that has from one to six carbon atoms. Non-limiting examples of alkylene groups include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), n-propylene ($-CH_2CH_2CH_2-$), isopropylene ($-CH_2CH(CH_3)-$), and the like.

The term "arylalkoxy" refers to an alkoxy substituted with aryl.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-4 ring heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and the remainder ring atoms being carbon (with appropriate hydrogen atoms unless otherwise indicated). Heteroaryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heteroaryl group may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, 1-oxo-pyridyl, furanyl, benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, imidazolyl thiazolyl, isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, indazolyl, benzoxazolyl, benzofuryl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, and benzo(b)thienyl, 3H-thiazolo[2,3-c][1,2,4]thiadiazolyl, imidazo[1,2-d]-1,2,4-thiadiazolyl,

imidazo[2,1-b]-1,3,4-thiadiazolyl, 1H,2H-furo[3,4-d]-1,2,3-thiadiazolyl, 1H-pyrazolo[5,1-c]-1,2,4-triazolyl, pyrrolo[3,4-d]-1,2,3-triazolyl, cyclopentatriazolyl, 3H-pyrrolo[3,4-c]isoxazolyl, 1H,3H-pyrrolo[1,2-c]oxazolyl, pyrrolo[2,1b]oxazolyl, and the like.

As used herein, the term "heteroaralkyl" or "heteroarylalkyl" means a heteroaryl group that is attached to another group by a (C_1-C_6)alkylene. Heteroaralkyl groups may be optionally substituted, either on the heteroaryl portion of the heteroaralkyl group or on the alkylene portion of the heteroaralkyl group, with one or more substituent. Representative heteroaralkyl groupss include 2-(pyridin-4-yl)-propyl, 2-(thien-3-yl)-ethyl, imidazol-4-yl-methyl and the like.

The term "heterocycloalkyl" refers to a nonaromatic 3-8 membered monocyclic, 7-12 membered bicyclic, or 10-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, S, B, P or Si, wherein the nonaromatic ring system is completely saturated.. Heterocycloalkyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heterocycloalkyl group may be substituted by a substituent. Representative heterocycloalkyl groups include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 4-piperidonyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane, tetrahydrofuranyl, tetrahydrothienyl, thiirene.

The term "heterocyclyl" refers to a nonaromatic 5-8 membered monocyclic, 7-12 membered bicyclic, or 10-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, S, B, P or Si, wherein the nonaromatic ring system has some degree of unsaturation. Heterocyclyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heterocyclyl group may be substituted by a substituent. Examples of these groups include thiirenyl, thiadiazirinyl, dioxazolyl, 1,3-oxathiolyl, 1,3-dioxolyl, 1,3-dithiolyl, oxathiazinyl, dioxazinyl, dithiazinyl, oxadiazinyl, thiadiazinyl, oxazinyl, thiazinyl, 1,4-oxathiin,1,4-dioxin, 1,4-dithiin, 1H-pyranyl, oxathiepinyl, 5H-1,4-dioxepinyl, 5H-1,4-dithiepinyl, 6H-isoxazolo[2,3-d]1,2,4-oxadiazolyl, 7aH-oxazolo[3,2-d]1,2,4-oxadiazolyl, and the like.

The term "alkylamino" refers to an amino substituent which is further substituted with one or two alkyl groups. The term "aminoalkyl" refers to an alkyl substituent which is further substituted with one or more amino groups. The term "mercaptoalkyl" refers to an

alkyl substituent which is further substituted with one or more mercapto groups. The term "hydroxyalkyl" or "hydroxylalkyl" refers to an alkyl substituent which is further substituted with one or more hydroxyl groups. The term "sulfonylalkyl" refers to an alkyl substituent which is further substituted with one or more sulfonyl groups. The term "sulfonylaryl" refers to an aryl substituent which is further substituted with one or more sulfonyl groups. The term "alkylcarbonyl" refers to an –C(O)-alkyl. The term "mercaptoalkoxy" refers to an alkoxy substituent which is further substituted with one or more mercapto groups. The term "alkylcarbonylalkyl" refers to an alkyl substituent which is further substituted with -C(O)-alkyl. The alkyl or aryl portion of alkylamino, aminoalkyl, mercaptoalkyl, hydroxyalkyl, mercaptoalkoxy, sulfonylalkyl, sulfonylaryl, alkylcarbonyl, and alkylcarbonylalkyl may be optionally substituted with one or more substituents.

Acids and bases useful in the methods herein are known in the art. Acid catalysts are any acidic chemical, which can be inorganic (e.g., hydrochloric, sulfuric, nitric acids, aluminum trichloride) or organic (e.g., camphorsulfonic acid, p-toluenesulfonic acid, acetic acid, ytterbium triflate) in nature. Acids are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions. Bases are any basic chemical, which can be inorganic (e.g., sodium bicarbonate, potassium hydroxide) or organic (e.g., triethylamine, pyridine) in nature. Bases are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions.

Alkylating agents are any reagent that is capable of effecting the alkylation of the functional group at issue (e.g., oxygen atom of an alcohol, nitrogen atom of an amino group). Alkylating agents are known in the art, including in the references cited herein, and include alkyl halides (e.g., methyl iodide, benzyl bromide or chloride), alkyl sulfates (e.g., methyl sulfate), or other alkyl group-leaving group combinations known in the art. Leaving groups are any stable species that can detach from a molecule during a reaction (e.g., elimination reaction, substitution reaction) and are known in the art, including in the references cited herein, and include halides (e.g., I-, Cl-, Br-, F-), hydroxy, alkoxy (e.g., -OMe, -O-t-Bu), acyloxy anions (e.g., -OAc, $-OC(O)CF_3$), sulfonates (e.g., mesyl, tosyl), acetamides (e.g., -NHC(O)Me), carbamates (e.g., N(Me)C(O)Ot-Bu), phosphonates (e.g., $-OP(O)(OEt)_2$), water or alcohols (protic conditions), and the like.

As used herein the term "substituent" or "substituted" means that a hydrogen radical on a compound or group (such as, for example, alkyl, alkenyl, alkynyl, alkylene, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, or heterocyclyl group) is replaced with any desired group that do not substantially adversely affect the stability of the

compound. In one embodiment, desired substituents are those which do not adversely affect the activity of a compound. A substituent that substantially affects the activity of a compound is one that causes the IC_{50} of the compound to be greater than 100 μM. In preferred embodiments, a compound of the invention has an IC_{50} in an assay indicative of activity useful for treatment of IL-12, IL-23, or IL-27-related dieases or conditions. Such assays are known to one of ordinary skill in the art, and include, e.g., the assays described herein, e.g., the assays of Examples 2-4. In preferred embodiments, the assay is the assay of Example 2 and the compound has an IC_{50} less than 1.0 mM, more preferably less than 100 uM, more preferably less than 10 uM, more preferably less than 1 uM, more preferably less than 100 nM, and more preferably less than 10 nM. The term "substituted" refers to one or more substituents (which may be the same or different), each replacing a hydrogen atom. Examples of substituents include, but are not limited to, halogen (F, Cl, Br, or I), hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo (i.e., carbonyl), thio, imino, formyl, carbamido, carbamyl, carboxyl, thioureido, thiocyanato, sulfoamido, sulfonylalkyl, sulfonylaryl, alkyl, alkenyl, alkoxy, mercaptoalkoxy, aryl, heteroaryl, cyclyl, heterocyclyl, wherein alkyl, alkenyl, alkyloxy, aryl, heteroaryl, cyclyl, and heterocyclyl are optionally substituted with alkyl, aryl, heteroaryl, halogen, hydroxyl, amino, mercapto, cyano, nitro, oxo (=O), thioxo (=S), or imino (=NR).

In other embodiments, substituents on any group (such as, for example, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, and heterocyclyl) can be at any atom of that group, wherein any group that can be substituted (such as, for example, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, and heterocyclyl) can be optionally substituted with one or more substituents (which may be the same or different), each replacing a hydrogen atom. Examples of suitable substituents include, but not limited to alkyl, alkenyl, alkynyl, cyclyl, cycloalkyl, heterocyclyl, heterocycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, halogen, haloalkyl, cyano, nitro, alkoxy, aryloxy, hydroxyl, hydroxylalkyl, oxo (i.e., carbonyl), carboxyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, heteroaryloxy, heteroaryloxycarbonyl, thio, mercapto, mercaptoalkyl, arylsulfonyl, amino, aminoalkyl, dialkylamino, alkylcarbonylamino, alkylaminocarbonyl, or alkoxycarbonylamino; alkylamino, arylamino, diarylamino, alkylcarbonyl, or arylamino-substituted aryl; arylalkylamino, aralkylaminocarbonyl, amido, alkylaminosulfonyl, arylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, imino,

carbamido, carbamyl, thioureido, thiocyanato, sulfoamido, sulfonylalkyl, sulfonylaryl, or mercaptoalkoxy.

Additional suitable substituents are alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, and heterocyclyl and include, without limitation halogen, CN, NO_2, OR^{15}, SR^{15}, $S(O)_2OR^{15}$, $NR^{15}R^{16}$, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, (=O), (=S), (=NR^{15}), $C(O)OR^{15}$, $C(O)NR^{15}R^{16}$, $OC(O)NR^{15}R^{16}$, $NR^{15}C(O)NR^{15}R^{16}$, $C(NR^{16})NR^{15}R^{16}$, $NR^{15}C(NR^{16})NR^{15}R^{16}$, $S(O)_2NR^{15}R^{16}$, R^{17}, C(O)H, $C(O)R^{17}$, $NR^{15}C(O)R^{17}$, $Si(R^{15})_3$, $OSi(R^{15})_3$, $Si(OH)_2R^{15}$, $B(OH)_2$, $P(O)(OR^{15})_2$, $S(O)R^{17}$, or $S(O)_2R^{17}$. Each R^{15} is independently hydrogen, C_1-C_6 alkyl optionally substituted with cycloalkyl, aryl, heterocyclyl, or heteroaryl. Each R^{16} is independently hydrogen, C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each R^{17} is independently C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl and C_1-C_4 alkyl in each R^{15}, R^{16} and R^{17} can optionally be substituted with halogen, CN, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, COOH, $C(O)OC_1$-C_4 alkyl, NH_2, C_1-C_4 alkylamino, or C_1-C_4 dialkylamino.

As used herein, the term "lower" refers to a group having up to six atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 6 carbon atoms, and a "lower alkenyl" or "lower alkynyl" refers to an alkenyl or alkynyl radical having from 2 to 6 carbon atoms, respectively.

Note that unless otherwise depicted, the left atom shown in any substituted group which has one point of attachment described above is the point of attachment.

In the compounds represented by formula (I), when n is 2 or greater, a compound of the invention may have two or more different $C(R^2R^4)$ moieties. When there is more than one group having a designation (e.g., R^c-, or R^d-containing substituted groups) in a compound of the invention, the moieties (e.g., R^c , R^d) can be the same or different. The same rules apply to other R-groups (e.g., R, R^g, R^h, R^j, R^k, etc).

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating IL-12 overproduction-related disorders such as rheumatoid arthritis, sepsis, Crohn's disease, multiple sclerosis, psoriasis, or insulin-dependent diabetes mellitus). The compounds produced by the methods herein can be incorporated into compositions, including solutions, capsules, crèmes, or ointments for administration to a subject (e.g., human, animal). Such compositions (e.g., pharmaceuticals) are useful for providing to the subject desirable health or other physiological benefits that are associated with such compounds.

Nucleophilic agents are known in the art and are described in the chemical texts and treatises referred to herein. The chemicals used in the aforementioned methods may include, for example, solvents, reagents, catalysts, protecting group and deprotecting group reagents and the like. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compound of the formulae described herein. The methods delineated herein contemplate converting compounds of one formula to compounds of another formula. The process of converting refers to one or more chemical transformations, which can be performed *in situ*, or with isolation of intermediate compounds. The transformations can include reacting the starting compounds or intermediates with additional reagents using techniques and protocols known in the art, including those in the references cited herein. Intermediates can be used with or without purification (e.g., filtration, distillation, crystallization, chromatography). Other embodiments relate to the intermediate compounds delineated herein, and their use in the methods (e.g., treatment, synthesis) delineated herein.

The compounds of this invention include the compounds themselves, as well as their salts, solvate, clathrate, hydrate, polymorph, or prodrugs, if applicable. As used herein, the term "pharmaceutically acceptable salt," is a salt formed from, for example, an acid and a basic group of a compound of any one of the formulae disclosed herein. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, besylate,

gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of any one of the formulae disclosed herein having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of any one of the formulae disclosed herein having a basic functional group, such as an amino functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid (HCl), hydrogen bromide (HBr), hydrogen iodide (HI), nitric acid, hydrogen bisulfide, phosphoric acid, lactic acid, salicylic acid, tartaric acid, bitartratic acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, and *p*-toluenesulfonic acid.

As used herein, the term "polymorph" means solid crystalline forms of a compound of the present invention or complex thereof. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (*e.g.*, to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (*e.g.*, tablets of one polymorph are

more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

As used herein, the term "hydrate" means a compound of the present invention or a salt thereof, which further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein, the term "clathrate" means a compound of the present invention or a salt thereof in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide a compound of this invention. Prodrugs may only become active upon such reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of any one of the formulae disclosed herein that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds of any one of the formulae disclosed herein that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed).

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide", "biohydrolyzable ester", "biohydrolyzable carbamate", "biohydrolyzable carbonate", "biohydrolyzable ureide" and "biohydrolyzable phosphate analogue" mean an amide, ester, carbamate, carbonate, ureide, or phosphate analogue, respectively, that either: 1) does not destroy the biological activity of the compound and confers upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is itself biologically inactive but is converted *in vivo* to a biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable

carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

In addition, some of the heteroaryl hydrazone compounds of this invention have one or more double bonds, or one or more asymmetric centers. Such compounds can occur as racemates, racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- or *E*- or *Z*- double isomeric forms. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Further, the aforementioned heteroaryl hydrazone compounds also include their *N*-oxides. The term "*N*-oxides" refers to one or more nitrogen atoms, when present in a heterocyclic or heteroaryl compound, are in *N*-oxide form, i.e., N→O. In particular, in compounds of formula (I), when one of Q, U, or V is N, also included are compounds in which Q, U, or V, respectively, is N→O. The compounds and compositions described herein are useful to treat and prevent any IL-12 production-related disorders, *e.g.*, inflammatory disorders, immune diseases, and bone loss diseases.

Also within the scope of this invention is a pharmaceutical composition that contains one or more of the heteroaryl hydrazone compounds of this invention and a pharmaceutically acceptable carrier.

The compounds and compositions described herein are useful to treat and prevent any IL-12 production-related disorders, *e.g.*, inflammatory disorders, immune diseases, and bone loss diseases.

The term "inflammatory disorders" includes any inflammatory disease, disorder or condition caused, exasperated or mediated by IL-12 production. Such inflammatory disorders may include, without limitation, asthma, adult respiratory distress syndrome, systemic lupus erythematosus, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), multiple sclerosis, insulin-dependent diabetes mellitus, autoimmune arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis),

inflammatory pulmonary syndrome, pemphigus vulgaris, idiopathic thrombocytopenic purpura, autoimmune meningitis, myasthenia gravis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome (including keratoconjunctivitis sicca secondary to Sjogren's Syndrome), alopecia areata, allergic responses due to arthropod bite reactions, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions (such as Stevens-Johnson syndrome), leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Graves ophthalmopathy, primary biliary cirrhosis, uveitis posterior and interstitial lung fibrosis.

"Inflammatory disorders" expressly include acute inflammatory disorders. Examples of acute inflammatory disorders include graft versus host disease, transplant rejection, septic shock, endotoxemia, Lyme arthritis, infectious meningitis (*e.g.*, viral, bacterial, Lyme disease-associated), an acute episode of asthma and acute episodes of an autoimmune disease.

"Inflammatory disorders" expressly include chronic inflammatory disorders. Nonlimiting examples of chronic inflammatory disorder include asthma, rubella arthritis, and chronic autoimmune diseases, such as systemic lupus erythematosus, psoriasis, inflammatory bowel disease, including Crohn's disease and ulcerative colitis, multiple sclerosis and rheumatoid arthritis.

The term "immune diseases" includes any immune disease, disorder or condition caused, exasperated or mediated by IL-12 production. Such immune diseases may include, without limitation, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory

distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disesease, thrombocytopenia, graft rejection of any organ or tissue, kidney translplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-meditated cytotoxicity, type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary billiary cirrhosis, vitiligo, vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, anti-cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (*e.g.*, including but not limited toasthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like. See, *e.g.*, the Merck Manual, 12th-17th Editions, Merck & Company, Rahway, N.J. (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells *et al.*, eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

The term "bone loss disease" includes any bone loss disease, disorder or condition caused, exasperated or mediated by IL-12 production *e.g.*, periodontal disease, non-malignant bone disorders (*e.g.*, osteoporosis, Paget's disease of bone, osteogenesis imperfecta, fibrous

dysplasia, and primary hyperparathyroidism), estrogen deficiency, inflammatory bone loss, bone malignancy, arthritis, osteopetrosis, and certain cancer-related disorders (*e.g.*, hypercalcemia of malignancy (HCM), osteolytic bone lesions of multiple myeloma and osteolytic bone metastases of breast cancer and other metastatic cancers.

The term "neurological disorder" refers to any neurological disease, disorder or condition caused, exasperated or mediated by IL-12 production. Examples of such neurological disorders include, without limitation, neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one TNF antibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16, Edition, Merck & Company, Rahway, N.J. (1992)

In the case of overlap in these definitions, the disease, condition or disorder may be considered to be a member of any of the above listed classes of IL-12 overproduction-related disorders. In one embodiment, IL-12 overproduction related diseases include rheumatoid

arthritis, sepsis, Crohn's disease, multiple sclerosis, psoriasis, or insulin-dependent diabetes mellitus.

The compounds and compositions described herein are useful to treat and prevent any IL-12 production-related disorders, *e.g.*, inflammatory disorders, immune diseases, and bone loss diseases. The method involves administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph, or prodrug thereof, to a subject in need of treatment of IL-12 overproduction related diseases. In preferred embodiments, treatment according to the invention provides a reduction in or prevention of at least one symptom or manifestation of an IL-12-, IL-23-, or IL-27-related disorder (e.g., inflammatory disorder, immune diseases, or bone loss disease), as determined *in vivo* or *in vitro* of at least about 10%, more preferably 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98% or 99%.

As used herein, the term "effective amount" refers to an amount of a compound of this invention which is sufficient to reduce or ameliorate the severity, duration, progression, or onset of an inflammatory disorder, immune diseases, or bone loss disease, prevent the advancement of an inflammatory disorder, immune diseases, or bone loss disease, cause the regression of an inflammatory disorder, immune diseases, or bone loss disease, prevent the recurrence, development, onset or progression of a symptom associated with an inflammatory disorder, immune diseases, or bone loss disease, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich *et al.*, (1966) *Cancer Chemother Rep* 50: 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardley, N.Y., 1970, 537. An effective amount of the heterocyclic compound of this invention can range from about 0.001 mg/kg to about 1000 mg/kg, more preferably 0.01 mg/kg to about 100 mg/kg, more preferably 0.1 mg/kg to about 10 mg/kg; or any range in which the low end of the range is any amount between 0.001 mg/kg and 900 mg/kg and the upper end of the range is any amount between 0.1 mg/kg and 1000 mg/kg (e.g., 0.005 mg/kg and 200 mg/kg, 0.5 mg/kg and 20 mg/kg). Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments such as use of other agents.

To practice the method of the present invention, a compound disclosed herein, as a component of a pharmaceutical composition, can be administered orally, parenterally, by

inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

A sterile injectable composition, for example, a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

A composition for oral administration can be any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation composition can be prepared according to techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. A heterocyclic compound of this invention can also be administered in the form of suppositories for rectal administration.

The carrier in the pharmaceutical composition must be "acceptable" in the sense of being compatible with the active ingredient of the formulation (and preferably, capable of stabilizing it) and not deleterious to the subject to be treated. For example, solubilizing agents such as cyclodextrins, which form specific, more soluble complexes with the compounds of this invention, or one or more solubilizing agents, can be utilized as pharmaceutical excipients for delivery of the heteroaryl hydrazone compounds of the invention. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

As used herein, the terms "animal", "subject" and "patient", include, but are not limited to, a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human (preferably, a human).

The biological activities of the compounds of the invention can be evaluated by a number of cell-based assays. One of such assays can be conducted using cells from human peripheral blood mononuclear cells (PBMC) or human monocytic cell line (THP-1). The cells are stimulated with a combination of human interferon-γ (IFNγ) and lipopolysaccharide or a combination of IFNγ and *Staphylococcus aureus* Cowan I in the presence of a test compound. The level of inhibition of IL-12 production can be measured by determining the amount of p70 by using a sandwich ELISA assay with anti-human IL-12 antibodies. IC_{50} of the test compound can then be determined. Specifically, PBMC or THP-1 cells are incubated with the test compound. Cell viability was assessed using the bioreduction of MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium] (Promega, Madison, WI).

A compound of the invention can also be evaluated by animal studies. For example, one of such studies involves the ability of a test compound to treat adjuvant arthritis (i.e., a IL-12 overproduction related disorder) in rats.

In certain embodiments, pharmaceutical compositions and dosage forms of the invention comprise one or more active ingredients in relative amounts and formulated in such a way that a given pharmaceutical composition or dosage form inhibits the uptake of calcium. Preferred pharmaceutical compositions and dosage forms comprise a compound of formula (I), or a pharmaceutically acceptable prodrug, salt, solvate, or clathrate thereof, optionally in combination with one or more additional active agents.

The methods for treating or preventing disorders associated with excessive bone loss in a patient in need thereof can further comprise administering to the patient being administered a compound of this invention, an effective amount of one or more other

therapeutic agents. Such therapeutic agents may include other therapeutic agents such as those conventionally used to prevent or treat disorders associated with excessive bone resorption or symptoms thereof. For example, such other agents include anti-resorptive agents for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen (such as Premarin®), estrogen/progestin combinations, and estrogen derivatives (such as estrone, estriol or 17α, 17β-ethynyl estradiol).

In such combination therapy treatment, both the compounds of this invention and the other drug agent(s) are administered to mammals (e.g., humans, male or female) by conventional methods. The agents may be administered in a single dosage form or in separate dosage forms. Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention where another therapeutic agent is administered to an animal, the effective amount of the compound of this invention is less than its effective amount would be where the other therapeutic agent is not administered. In another embodiment, the effective amount of the conventional agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, dthynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogesterone, hydroxyprogesterone, caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, and tigestol. Preferred progestins are medroxyprogestrone, norethindrone and norethynodrel.

Exemplary bone resorption inhibiting polyphosphonates include polyphosphonates of the type disclosed in U.S. Pat. No. 3,683,080. Preferred polyphosphonates are geminal dipolyphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonate. Ibandronic acid is an especially preferred

polyphosphonate. Alendronate is an especially preferred polyphosphonate. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-1-hydroxy-hexylidene- biphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1- diphosphonic acid, propane-N,N-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl)amino methane diphosphonic acid, butane-4-amino-1- hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy-1,1-diphosphonic acid, hexane-6-amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

In particular, the compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Any estrogen agonist/antagonist may be used for this purpose. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and/or prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue; and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods, and E. F Eriksen et al., Bone Histomorphometry, Raven Press, New York, pp. 1-74 (1994); S. J. Grier et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol. 31(1): 50-62 (1996); Wahner H. W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London, pp. 1-296 (1994)). A variety of these compounds are described and referenced below.

A preferred estrogen agonist/antagonist is droloxifene: (phenol, 3-(1-(4-(2-(dimethylamino)ethoxy)phenyl)-2-phenyl-1-butenyl)-, (E)-) and related compounds which are disclosed in U.S. Pat. No. 5,047,431. Another preferred estrogen agonist/antagonist is 3-

(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, which is disclosed in Wilson et al., Endocrinology 138: 3901-11 (1997). Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine,2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and related compounds which are disclosed in U.S. Pat. No. 4,536,516. Another related compound is 4-hydroxy tamoxifen which is disclosed in U.S. Pat. No. 4,623,660.

A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)etho xy)phenyl)hydrochloride) which is disclosed in U.S. Pat. No. 4,418,068. Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. Pat. No. 4,996,225. Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(-methoxy-2,2,dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-pyrrolidine, which is disclosed in U.S. Pat. No. 3,822,287. Also preferred is levormeloxifene. Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrol idinone, which is disclosed in U.S. Pat. No. 4,839,155. Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiop hen-6-ol which is disclosed in U.S. Pat. No. 5,488,058. Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol which is disclosed in U.S. Pat. No. 5,484,795. Another preferred estrogen agonist/antagonist is (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2- (4-hydroxy-phenyl)-benzo[b]thiop hen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc. Other preferred estrogen agonist/antagonists include compounds as described in U.S. Pat. No. 5,552,412. Especially preferred compounds described therein are: cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)- 5,6,7,8-tetr ahydro-naphthalene-2-ol; (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro -naphthalene-2-ol; cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8- tetrahydro-nap hthalene-2-ol; cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6- hydroxy-1,2,3,4-tetrahyd ronaphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"- fluorophenyl)-6-hydroxy-1,2,3,4-tetrah ydroisoquinoline; cis-6-(4-hydroxyphenyl)- 5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetr ahydro-naphthalene-2-ol; and 1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline. Other estrogen agonist/antagonists are described in U.S. Pat.

No. 4,133,814. U.S. Pat. No. 4,133,814 discloses derivatives of 2-phenyl-3-aroyl-benzothiophene and 2-phenyl-3-aroylbenzothiophene-1-oxide.

Those skilled in the art will recognize that other bone anabolic agents, also referred to as bone mass augmenting agents, may be used in conjunction with the compounds of this invention. A bone mass augmenting agent is a compound that augments bone mass to a level which is above the bone fracture threshold as detailed in the World Health Organization Study World Health Organization, "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis (1994). Report of a WHO Study Group. World Health Organization Technical Series 843." Any prostaglandin, or prostaglandin agonist/antagonist may be used in combination with the compounds of this invention. Those skilled in the art will recognize that IGF-1, sodium fluoride, parathyroid hormone (PTH), active fragments of parathyroid hormone, growth hormone or growth hormone secretagogues may also be used. The following paragraphs describes in greater detail exemplary compounds that may be administered in combination with compounds of this invention

Prostaglandins: The term prostaglandin refers to compounds which are analogs of the natural prostaglandins PGD_1, PGD_2, PGE_2, PGE_1 and PGF_2 which are useful in the treatment of osteoporosis and other disorders associated with excessive osteoclastic bone resorption. These compounds bind to the prostaglandins receptors. Such binding is readily determined by those skilled in the art of standard assays (e.g., S. An et al., Cloning and Expression of the EP_2 Subtype of Human Receptors for Prostaglandin E_2 Biochemical and Biophysical Research Communications, 197(1): 263-270 (1993)).

Prostaglandins are alicyclic compounds related to the basic compound prostanoic acid. The carbon atoms of the basic prostaglandin are numbered sequentially from the carboxylic carbon atom through the cyclopentyl ring to the terminal carbon atom on the adjacent side chain. Normally the adjacent side chains are in the trans orientation. The presence of an oxo group at C-9 of the cyclopentyl moiety is indicative of a prostaglandin within the E class while PGE_2 contains a trans unsaturated double bond at the C_{13}-C_{14} and a cis double bond at the C_5 –C_6 position.

A variety of prostaglandins are described and referenced below. However, other prostaglandins will be known to those skilled in the art. Exemplary prostaglandins are disclosed in U.S. Pat. Nos. 4,171,331 and 3,927,197,. Norrdin et al., The Role of Prostaglandins in Bone in Vivo, Prostaglandins Leukotriene Essential Fatty Acids 41: 139-150 (1990) is a review of bone anabolic prostaglandins. Any prostaglandin agonist/antagonist may be used in combination with the compounds of this invention. The

term prostaglandin agonist/antagonist refers to compounds which bind to prostaglandin receptors (eg., An S. et al., Cloning and Expression of the EP_2 Subtype of Human Receptors for Prostaglandin E_2, Biochemical and Biophysical Research Communications 197(1): 263-70 (1993)) and mimic the action of prostaglandin in vivo (e.g., stimulate bone formation and increase bone mass). Such actions are readily determined by those skilled in the art of standard assays. Eriksen E. F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pp. 1-74; S.J. Grier et al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol. 31(1): 50-62 (1996); H. W. Wahner and I. Fogelman, The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice, Martin Dunitz Ltd. London, pp. 1-296 (1994). A number of these compounds are described and reference below. However, other prostaglandin agonists/antagonists will be known to those skilled in the art. Exemplary prostaglandin agonists/antagonists are disclosed as follows. U.S. Pat. No. 3,932,389 discloses 2-descarboxy-2-(tetrazol-5-yl)-11-desoxy-15-substituted-omega-pentanorpros taglandins useful for bone formation activity. U.S. Pat. No. 4,018,892, discloses 16-aryl-13,14-dihydro-PGE_2 p-biphenyl esters useful for bone formation activity. U.S. Pat. No. 4,219,483, discloses 2,3,6-substituted-4-pyrones useful for bone formation activity. U.S. Pat. No. 4,132,847, discloses 2,3,6-substituted-4-pyrones useful for bone formation activity. U.S. Pat. No. 4,000,309, discloses 16-aryl-13,14-dihydro-PGE_2 p-biphenyl esters useful for bone formation activity. U.S. Pat. No. 3,982,016, discloses 16-aryl-13,14-dihydro-PGE_2 p-biphenyl esters useful for bone formation activity. U.S. Pat. No. 4,621,100, discloses substituted cyclopentanes useful for bone formation activity. U.S. Pat. No. 5,216,183, discloses cyclopentanones useful for bone formation activity.

Sodium fluoride may be used in combination with the compounds of this invention. The term sodium fluoride refers to sodium fluoride in all its forms (e.g., slow release sodium fluoride, sustained release sodium fluoride). Sustained release sodium fluoride is disclosed in U.S. Pat. No. 4,904,478. The activity of sodium fluoride is readily determined by those skilled in the art of biological protocols.

Bone morphogenetic protein may be used in combination with the compounds of this invention (e.g., see Ono et al., Promotion of the Osteogenetic Activity of Recombinant Human Bone Morphogenetic Protein by Prostaglandin E_1, Bone 19(6): 581-588 (1996)).

Any parathyroid hormone (PTH) may be used in combination with the comound of this invention. The term parathyroid hormone refers to parathyroid hormone, fragments or metabolites thereof and structural analogs thereof which can stimulate bone formation and increase bone mass. Also included are parathyroid hormone related peptides and active

fragments and analogs of parathyroid related peptides (see PCT publication No. WO 94/01460). Such bone anabolic functional activity is readily determined by those skilled in the art of standard assays. A variety of these compounds are described and referenced below. However, other parathyroid hormone will be known to those skilled in the art. Exemplary parathyroid hormones are disclosed in the following references. "Human Parathyroid Peptide Treatment of Vertebral Osteoporosis", Osteoporosis Int., 3, (Supp 1): 199-203. "PTH 1-34 Treatment of Osteoporosis with Added Hormone Replacement Therapy: Biochemical, Kinetic and Histological Responses" Osteoporosis Int. 1: 162-170.

Any growth hormone or growth hormone secretagogue may be used in combination with the compounds of this invention. The term growth hormone secretagogue refers to a compound which stimulates the release of growth hormone or mimics the action of growth hormone (e.g., increases bone formation leading to increased bone mass). Such actions are readily determined by those skilled in the art of standard assays well known to those of skill in the art. A variety of these compounds are disclosed in the following published PCT patent applications: WO 95/14666; WO 95/13069; WO 94/19367; WO 94/13696; and WO 95/34311. However, other growth hormones or growth hormone secretagogues will be known to those skilled in the art. In particular, a preferred growth hormone secretagogue is N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-y l)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:MK-667. Other preferred growth hormone secretagogues include 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo- [4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide or its L-tartaric acid salt; 2-amino-N-(1-(R)-benzyloxymethyl-2-(3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo -2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl)isobutyram ide; 2-amino-N-(2-(3a-(R)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyr idin-5-yl)-1-(R)benzyloxymethyl-2-oxo-ethyl)isobutyramide; and 2-amino-N-(1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-pyridin-2-ylm ethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyrid in-5-yl)-ethyl)-2-methyl-propionamide.

The other therapeutic agent can be a steroid or a non-steroidal anti-inflammatory agent. Useful non-steroidal anti-inflammatory agents, include, but are not limited to, aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac,

oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam; salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone and pharmaceutically acceptable salts thereof and mixtures thereof. For a more detailed description of the NSAIDs, *see Paul A. Insel, Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

For arthritis, inflammation-mediated bone loss and other disorders that have an inflammatory component, preferred conventional treatments for use in combination therapy with the compounds and compositions of this invention include (without limitation) naproxen sodium (Anaprox® and Anaprox® DS, Roche), flurbiprofen (Ansaid®; Pharmacia), diclofenac sodium + misoprostil (Arthrotec®, Searle), valdecoxib (Bextra®, Pharmacia), diclofenac potassium (Cataflam® and Voltaren®, Novartis), celecoxib (Celebrex®, Pharmacia), sulindac (Clinoril®, Merck), oxaprozin (Daypro®, Pharmacia), salsalate (Disalcid®, 3M), diflunisal (Dolobid®, Merck), naproxen sodium (EC Naprosyn®, Roche), piroxicam (Feldene®, Pfizer), indomethacin (Indocin® and Indocin SR®, Merck), etodolac (Lodine® and Lodine XL®, Wyeth), meloxicam (Mobic®, Boehringer Ingelheim), ibuprofen (Motrin®, Pharmacia), naproxen (Naprelan®, Elan), naproxen (Naprosyn®, Roche), ketoprofen (Orudis® and Oruvail®, Wyeth), nabumetone (Relafen®, SmithKline), tolmetin sodium (Tolectin®, McNeil), choline magnesium trisalicylate (Trilisate®, Purdue Fredrick), and rofecoxib (Vioxx®, Merck).

In any case where pain in a component of the target disorder, the other therapeutic agent can be an analgesic. Useful analgesics include, but are not limited to, phenacetin, butacetin, acetaminophen, nefopam, acetoamidoquinone, and mixtures thereof.

For use against osteoporosis, Paget's disease and other disorders associated with bone deterioration, preferred conventional agents that mayu be used in combination with compounds and compositions of this invention include (without limitation) bisphosphonates (such as etidronate (Didronel®, Procter & Gamble), pamidronate (Aredia®, Novartis), and alendronate (Fosamax®, Merck)), tiludronate (Skelid®, Sanofi-Synthelabo, Inc.), risedronate (Actonel®, Procter & Gamble/Aventis), calcitonin (Miacalcin®), estrogens (Climara®, Estrace®, Estraderm®, Estratab®, Ogen®, Ortho-Est®, Vivelle®, Premarin®, and others) estrogens and progestins (Activella™, FemHrt®, Premphase®, Prempro®, and others), parathyroid hormone and portions thereof, such as teriparatide (Forteo®, Eli Lilly and Co.), selective estrogen receptor modulators (SERMs) (such as raloxifene (Evista®)) and treatments currently under investigation (such as other parathyroid hormones, sodium fluoride, vitamin D metabolites, and other bisphosphonates and selective estrogen receptor modulators).

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one compound of this invention to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating an IL-12 production related disorder, wherein the administering further comprises administering before, concurrently with, and/or after the compound of this invention, at least one additional active agent selected from a TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropieitin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a

cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, domase alpha (Pulmozyme), a cytokine or a cytokine antagonistm. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2.sup.nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are entirely incorporated herein by reference.

TNF antagonists suitable for compositions, combination therapy, co-administration, devices and/or methods of the present invention include, but are not limited to, anti-TNF antibodies (such as, Remicade (Infliximab) or Humira (adalimumab)) for example, or , antigen-binding fragments thereof, and receptor molecules which bind specifically to TNF (such as, for example, Enbrel (Etanercept)); compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g, pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen activated protein (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metalloproteinase inhibitors; compounds which block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril); and compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

For clarifiation, a "tumor necrosis factor antibody," "TNF antibody," "TNF antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNF activity in vitro, in situ and/or preferably in vivo. For example, a suitable TNF human antibody of the present invention can bind TNFa and includes anti-TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNFa. A suitable TNF anttibody or fragment can also decrease block, abrogate, interfere, prevent and/or inhibit TNF RNA, DNA or protein synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

The foregoing and other useful combination therapies will be understood and appreciated by those of skill in the art. Potential advantages of such combination therapies include the ability to use less of each of the individual active ingredients to minimize toxic

side effects, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Responsiveness of a particular condition, disease or disorder to compounds and compositions of this invention can be measured directly by comparison against conventional drugs, or can be inferred based on an understanding of disease etiology and progression. There are a number of cellular and bone resorption assay systems that are widely accepted in the art as predictive of in vivo effects. As the bone resorption assay uses material that includes all bone cells, it is an ex vivo assay. Thus, the showing that a compound of this invention inhibits bone resorption in these assays is evidence of the clinical utility of these for treating or preventing conditions associated with excessive bone loss. Various scientific publications (such as Carano et al. J. Clin. Invest. 85: 456-461 (1990); Blair & Schlesinger, The Biology and Physiology of the Osteoclast, CRC Press, Eds., Gay, C. V. and Rifkin, B. R., pp. 259-288 (1992); and Vaananen et al., J. Cell Biology 111: 1305-1311 (1990)) support the fact that such assays are accepted as being predictive of in vivo activity. Furthermore, the in vitro effects of Herbimycin A on bone resorption were shown to correlate with in vivo activity (Yoneda et al., J. Clin. Invest. 91: 2791-95 (1993)).

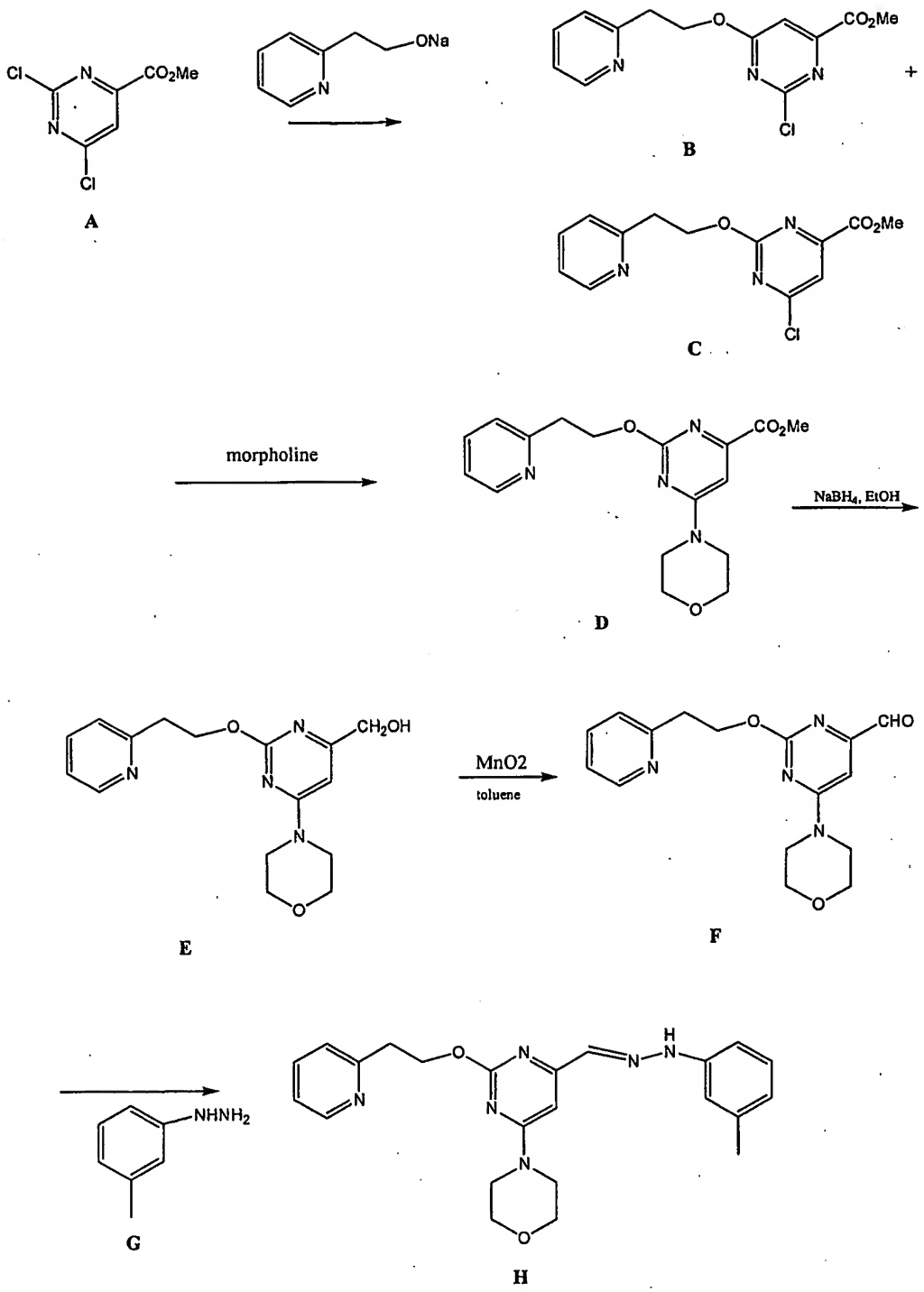
Without further elaboration, it is believed that the above description has adequately enabled the present invention. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All of the references and publications cited herein are hereby incorporated by reference in their entirety.

Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

The compounds described above can be prepared by methods well known in the art, as well as by the synthetic routes disclosed herein. For example, a heteroaryl hydrazone compound can be prepared by using methyl 2,4-dichloro-pyrimidine-6-carboxylate (compound A in Scheme 1 below) as a starting material. The two chloro groups can be displaced by various substitutes. More specifically, a first chloro group (e.g., at position 2 or 4) can react with, e.g., a metal alkoxide (e.g., sodium, potassium alkoxide), prepared from an alcohol with a base (e.g., NaH, KH). For example, exposure of compound **A** to the sodium salt of 2-pyridine ethanol (e.g., *via* 2-pyridine ethanol and NaH) affords a mixture of the isomeric pyrimidine ethers **B** and **C** (see Scheme 1 below). The remaining chloro group (e.g., at the 2 or 4 position) can be replaced with a nucleophile, e.g., a cyclic amine. For example,

treatment of the **B/C** isomer mixture with morpholine provides, after chromatography compound **D** (see Scheme 1 below). The hydrazone linkage can be formed by condensing a heteroaryl aldehyde with, e.g., an aryl or heteroaryl hydrazine. The heteroaryl aldehyde, e.g., **F**, may be obtained from a heteroaryl ester, e.g., **D** *via* a one or two step reduction sequence. For example, ester **D** can be reduced with sodium borohydride to give the primary alcohol **E**, which in turn can be oxidized with manganese dioxide to afford aldehyde **F** (see Scheme 1 below). Generally, hydrazones are prepared by heating a heteroaryl aldehyde, e.g., **F**, and an aryl or heteroaryl hydrazine, e.g., **G**, in ethanol with catalytic amount of acetic acid (see Scheme 1 below). The hydrazones can generally be isolated by column chromatography and/or recrystallization in quantitative yields. Thus, a heteroaryl hydrazone compound of this invention is obtained. If preferred, other types of linkages can be prepared by similar reactions. Sensitive moieties on a heteroaryl intermediate and a nucleophile can be protected prior to carrying out any of the reductions described herein.

SCHEME 1



The chemicals used in the above-described synthetic routes may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the heteroaryl hydrazone compounds. In addition, various

synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable heteroaryl hydrazone compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

A heteroaryl hydrazone compound thus obtained can be further purified by flash column chromatography, high performance liquid chromatography, or crystallization.

Correspondingly, pyridine, pyridinyl and triazinyl compounds described herein can be made according to methods know in the art, including those in the aforementioned treatises. The pyridinyl and triazinyl compounds can be made using analogous synthetic procedures and reagents as described for the pyrimidinyl compounds. It is recognized by one of ordinary skill that pyrimidines demonstrate reactivity intermediate relative to that of pyridines and triazines, therefore reaction conditions (e.g., temperature, reaction time, etc.) may be adjusted accordingly, which is routine for one of ordinary skill.

EXAMPLES

Example 1. General Procedure for the Preparation of Compounds **1-4** and **6**.

To a stirred solution of 2-pyridine-ethanol (1.82 g, 14.8 mmol) in anhydrous THF (30 mL) was added NaH (60% dispersion in mineral oil) at 0 °C under nitrogen purge, and stirring was continued for 30 minutes. The resulting solution was cannulated to a precooled (NaCl-ice bath), stirred solution of methyl 2,4-dichloro-pyrimidine-6-carboxylate, (2.92 g, 14.1 mmol) in THF (35 mL). After addition was complete, the reaction mixture was stirred at the NaCl-ice bath temperature for 45 minutes, then allowed to warm to room tempaerature. The reaction mixture was carefully quenched with water, then ethyl acetate was added. The ethyl acetate solution was washed with brine, dried, concentrated and purified by column chromatography to afford 1.6 g (41 %) of mixture of isomers. This isomer mixture was dissolved in dioxane and treated with morpholine (2eq, 0.98 mL) to form morpholine derivatives rapidly, which were separated by column chromatography to give 0.92 g of 2-(morpholin-4-yl)-4-[2-(pyridin-2-yl)-ethoxy]-6-methoxycarbonyl)-pyrimidine and 0.89g of 2-[2-(pyridin-2-yl)-ethoxy]-4-(methoxycarbonyl)-6-(morpholin-4-yl)-pyrimidine (96%).

Preparation of alcohol derivative used to prepare Compounds 1-4: To a solution of 2-[2-(pyridin-2-yl)-ethoxy]-4-(methoxycarbonyl)-6-(morpholin-4-yl)-pyrimidine (0.81 g, 2.35 mmol) in ethanol sodium borohydride (4 eq, 0.36 g) was added in portions and the reaction mixture was refluxed for 3 hours. Solvent was removed, the reaction mixture distributed between ethyl acetate and water, organic solution washed with brine, dried and concentrated to give crude alcohol. The above alcohol (0.64 g, 2 mmol) was heated in toluene at 85 °C with manganese dioxide, (10 eq, 1.75 g) for 4 hours to give 2-[2-(pyridin-2-yl)-ethoxy]-4-formyl-6-(morpholin-4-yl)-pyrimidine (0.3 g, 48 %) which was isolated by column chromatography.

Preparation of alcohol derivative used to prepare Compound 6: For Compound 6, the alcohol derivative was prepared as in the preceeding paragraph except that 2-(morpholin-4-yl)-4-[2-(pyridin-2-yl)-ethoxy]-6-methoxycarbonyl)-pyrimidine was used instead of 2-[2-(pyridin-2-yl)-ethoxy]-4-(methoxycarbonyl)-6-(morpholin-4-yl)-pyrimidine.

Hydrazones (light-yellow solids) were prepared from the aldehyde and aryl-hydrazines (i.e., m-tolyl hydrazine (Compounds 1 and 6), 3-chlorophenyl hydrazine (Compound 2), 3-methoxyphenyl hydrazine (Compound 3), and 2,5-dimethylphenyl hydrazine (Compound 4)) (1 eq) by brief heating of their solution in ethanol with catalytic amount of acetic acid in quantitative yields and isolated by column chromatography or recrystallization.

Analytical data for compound **1**, *N*-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-*N'*-*m*-tolyl-hydrazine: ^{1}H NMR ($CDCl_3$): δ 8.55 (d, J = 4.8 Hz,1H), 8.00 (s, 1H), 7.61 (td, J = 7.8 and 1.8 Hz 1H), 7.48 (s, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.21-7.12 (m, 2H), 6.94 (m, 2H), 6.76 (s, 1H), 6.74 (d, J = 6.3 Hz,1H), 4.69 (t, J = 6.9 Hz, 2H), 3.77 (m, 4H), 3.67 (m, 4H), 3.29 (t, J = 6.9 Hz, 2H), 2.34 (s, 3H); ESMS clcd for $C_{23}H_{26}N_6O_2$: 418.21; Found: 419.5 $(M+1)^+$.

Analytical data for compound **2**, *N*-(3-Chloro-phenyl)- *N'*-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine: ^{1}H NMR ($CDCl_3$): δ 8.71 (s, 1H), 8.52 (d, J = 4.2 Hz,1H), 7.57 (td, J = 6.3 and 0.9 Hz 1H), 7.49 (s, 1H), 7.25 (d, J = 9.0 Hz, 1H), 7.19-7.12 (m, 4H), 6.90 (m, 2H), 6.71 (s, 1H), 4.67 (t, J = 6.9 Hz, 2H), 3.77 (m, 4H), 3.66 (m, 4H), 3.26 (t, J = 6.9 Hz, 2H); ESMS clcd for $C_{22}H_{23}ClN_6O_2$: 438.16; Found: 439.4 $(M+1)^+$.

Analytical data for compound **3**, *N*-(3-Methoxy-phenyl)- *N'*-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine: ^{1}H NMR ($CDCl_3$): δ 8.54 (d, J = 5.1 Hz,1H), 8.34 (s, 1H), 7.59 (td, J = 9.0 and 1.8 Hz 1H), 7.48 (s, 1H), 7.28 (d, J = 6.0 Hz,

1H), 7.21-7.12 (m, 2H), 6.75 (m, 2H), 6.67 (d, J = 8.1 Hz, 1H), 6.74 (dd, J = 6.3 and 2.7 Hz,1H), 4.69 (t, J = 6.9 Hz, 2H), 3.81 (s, 3H), 3.78 (m, 4H), 3.66 (m, 4H), 3.28 (t, J = 6.9 Hz, 2H); ESMS clcd for $C_{23}H_{26}N_6O_2$: 434.49; Found: 435.4 $(M+1)^+$.

Analytical data for compound **4**, *N*-(2,5-Dimethyl-phenyl)- *N'*-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine: ^{1}H NMR ($CDCl_3$): δ 8.55 (d, J = 5.1 Hz,1H), 7.86 (s, 1H), 7.61 (td, J = 7.8 and 1.8 Hz 1H), 7.58 (s, 1H),7.32-7.28 (m, 2H), 7.14 (m, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.78 (s, 1H), 6.69 (d, J = 7.2 Hz,1H), 4.70 (t, J = 6.9 Hz, 2H), 3.80 (m, 4H), 3.68 (m, 4H), 3.32 (t, J = 6.9 Hz, 2H), 2.35 (s, 3H), 2.21 (s, 3H); ESMS clcd for $C_{24}H_{28}N_6O_2$: 432.23; Found: 433.5 $(M+1)^+$.

Analytical data for compound **6**, *N*-[2-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-*N'*-*m*-tolyl-hydrazine: ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 4.8 Hz,1H), 8.07 (s, 1H), 7.63 (td, J = 7.2 and 1.5 Hz 1H), 7.43 (s, 1H), 7.26 (d, J = 7.0 Hz, 1H), 7.18-7.13 (m, 2H), 6.96 (m, 1H), 6.89 (d, J = 8.1 Hz,1H), 6.73 (d, J = 7.5 Hz,1H), 6.57 (s, 1H), 4.70 (t, J = 6.9 Hz, 2H), 3.76 (m, 8H), 3.26 (t, J = 6.9 Hz, 2H), 2.33 (s, 3H); ESMS clcd for $C_{23}H_{26}N_6O_2$: 418.21; Found: 419.5 $(M+1)^+$.

Example 2. *In vitro* assays

Reagents. *Staphylococcus aureus* Cowan I (SAC) is obtained from Calbiochem (La Jolla, CA), and lipopolysaccharide (LPS, *Serratia marscencens*) is obtained from Sigma (St. Louis, MO). Human and mouse recombinant IFNγ are purchased from Boehringer Mannheim (Mannheim, Germany) and Pharmingen (San Diego, CA), respectively.

Human In Vitro Assay. Human PBMC were isolated by centrifugation using Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden) and prepared in RPMI medium supplemented with 10% fetal calf serum (FCS), 100 U/mL penicillin, and 100 μg/mL streptomycin. PBMC were plated in wells of a 96-well plate at a concentration of 5 x 10^5 cells/well, and primed by adding IFNγ (30 U/mL) for 22 h and stimulated by adding LPS (1 μg/mL), or by adding IFNγ (100 U/mL) and then stimulated by adding SAC (0.01%). A test heteroaryl hydrazone compound was dissolved in DMSO, and added to wells of the 96-well plate. The final DMSO concentration was adjusted to 0.25% in all cultures, including the compound-free control. Human THP-1 cells were plated in wells, primed by adding IFNγ (100 U/mL) for 22 h and stimulated by adding SAC (0.025%) in the presence of different concentrations of the heteroaryl hydrazone compound. Cell-free supernatants were taken 18 h later for measurement of cytokines. Cell viability was assessed using the bioreduction of MTS. Cell

survival was estimated by determining the ratio of the absorbance in compound-treated groups versus compound-free control.

The supernatant was assayed for the amount of IL-12p40, IL-12p70, or IL-10 by using a sandwich ELISA with anti-human antibodies, i.e., a Human IL-12 p40 ELISA kit from R&D Systems (Berkeley, CA), and a Human IL-12 p70 or IL-10 ELISA kit from Endogen (Cambridge, MA). Assays were based on the manufacturer's instructions.

Murine In Vitro Assay. Balb/c mice (Taconic, Germantown, NY) were immunized with *Mycobacterium tuberculosis* H37Ra (Difco, Detroit, MI). The splenocytes were harvested 5 days and prepared in RPMI medium supplemented with 10% FCS and antibiotics in a flat bottom 96-well plate with 1 x 10^6 cells/well. The splenocytes were then stimulated with a combination of IFNγ (60 ng/mL) and SAC (0.025%) [or LPS (20 μg/mL)] in the presence of a test compound. Cell-free supernatants were taken 24 h later for the measurement of cytokines. The preparation of compound and the assessment of cell viability were carried out as described above. Mouse IL-12 p70, IL-10, IL-1β, and TNFα were measured using ELISA kits from Endogen, according to the manufacturer's instructions.

The biological activities of heteroaryl hydrazone compounds were tested on human PBMC or THP-1 cells. IC^{50} values are shown in Table 1 below.

Table 1

Compound	IC^{50}
1	2.2 nM
2	10 nM
3	2.2 nM
4	6.5 nM
6	40 nM

Example 3. *In vivo* assays

Treatment of adjuvant arthritis in rats: Adjuvant arthritis (AA) is induced in female Lewis rats by the intracutaneous injection (base of the tail) of 0.1 mL of a 10 mg/mL bacterial suspension made from ground, heat-killed *Mycobacterium tuberculosis* H37Ra suspended in incomplete Freund's adjuvant. Rats are given a test compound orally once a day for 12 days, starting the day following the induction. The development of polyarthritis is monitored daily

by macroscopic inspection and assignment of an arthritis index to each animal, during the critical period (days 10 to 25 post-immunization).

The intensity of polyarthritis is scored according to the following scheme: (*a*) Grade each paw from 0 to 3 based on erythema, swelling, and deformity of the joints: 0 for no erythema or swelling; 0.5 if swelling is detectable in at least one joint; 1 for mild swelling and erythema; 2 for swelling and erythema of both tarsus and carpus; and 3 for ankylosis and bony deformity. Maximum score for all 4 paws was thus 12. (*b*) Grade for other parts of the body: for each ear, 0.5 for redness and another 0.5 if knots are present; 1 for connective tissue swelling (saddle nose); and 1 for the presence of knots or kinks in the tail. The highest possible arthritic index was 16.

Treatment of Crohn's disease in dinitrobenzene sulfonic acid-induced inflammatory bowel syndrome model rats: Wistar derived male or female rats weighing 200 ± 20 g and fasted for 24 hours are used. Distal colitis is induced by intra-colonic instillation of 2,4-dinitrobenzene sulfonic acid (DNBS, 25 mg in 0.5 mL ethanol 30%) after which air (2 mL) is gently injected through the cannula to ensure that the solution remained in the colon. A test compound and/or vehicle is administered orally 24 and 2 hours before DNBS instillation and then daily for 5 days. One control group is similarly treated with vehicle alone while the other is treated with vehicle plus DNBS. The animals were sacrificed 24 hours after the final dose of test compound administration and each colon is removed and weighed. Colon-to-body weight ratio is then calculated for each animal according to the formula: Colon (g)/BW × 100. The "Net" increase in ratio of Vehicle-control + DNBS group relative to Vehicle-control group is used as a base for comparison with test substance treated groups and expressed as "% Deduction."

Treatment of Crohn's disease in $CD4^+CD45Rb^{high}$ T cell-reconstituted SCID colitis model mice: Spleen cells are prepared from normal female BALB/c mice. For cell purification, the following anti-mouse antibodies were used to label non-$CD4^+$ T cells: B220 (RA3-6B2), CD11b (M1/70), and CD8α (53-6.72). All antibodies are obtained from BioSource (Camarillo, CA). M450 anti-rat IgG-coated magnetic beads (Dynal, Oslo, Norway) were used to bind the antibodies and negative selection was accomplished using an MPC-1 magnetic concentrator. The enriched $CD4^+$ cells are then labeled for cell sorting with FITC-conjugated CD45RB (16A, Pharmingen, San Diego, CA) and PE-conjugated CD4 (CT-CD4, Caltag, Burlingame, CA). $CD4^+$ $CD45RB^{high}$ cells are operationally defined as the upper 40% of CD45Rb-staining $CD4^+$ cells and sorted under sterile conditions by flow cytometry. Harvested cells are resuspended at 4×10^6/mL in PBS and injected 100 µL

intraperitoneally into female C.B-17 *SCID* mice. Heteroaryl hydrazone compounds of this invention (e.g., Compound 12) and/or vehicle is orally administered once a day, 5 days per week, starting the day following the transfer. The transplanted *SCID* mice are weighed weekly and their clinical condition is monitored.

Colon tissue samples are fixed in 10% buffered formalin and embedded in paraffin. Sections (4 μm) collected from ascending, transverse, and descending colon were cut and stained with hematoxylin and eosin. The severity of colitis was determined based on histological examination of the distal colon sections, whereby the extent of colonic inflammation is graded on a scale of 0-3 in each of four criteria: crypt elongation, cell infiltration, depletion of goblet cells, and the number of crypt abscesses.

LP lymphocytes are isolated from freshly obtained colonic specimens. After removal of payer's patches, the colon was washed in Ca/Mg-free HBSS, cut into 0.5 cm pieces and incubated twice in HBSS containing EDTA (0.75 mM), DTT (1 mM), and antibiotics (amphotericin 2.5 μg/mL, gentamicin 50 μg/mL from Sigma) at 37°C for 15 min. Next, the tissue is digested further in RPMI containing 0.5 mg/mL collagenase D, 0.01 mg/mL DNase I (Boehringer Manheim), and antibiotics at 37°C. LP cells are then layered on a 40-100% Percoll gradient (Pharmacia, Uppsala, Sweden), and lymphocyte-enriched populations are isolated from the cells at the 40-100% interface.

To measure cytokine production, 48-well plates were coated with 10 μg/mL murine anti-CD3ε antibody (145-2C11) in carbonate buffer (PH 9.6) overnight at 4°C. 5×10^5 LP cells are then cultured in 0.5ml of complete medium in precoated wells in the presence of 1 μg/mL soluble anti-CD28 antibody (37.51). Purified antibodies are obtained from Pharmingen. Culture supernatants are removed after 48 h and assayed for cytokine production. Murine IFNγ is measured using an ELISA kit from Endogen (Cambridge, MA), according to the manufacturer's instructions.

Example 4

Human peripheral blood mononuclear cells (PBMC) are isolated from healthy donor blood. The cells are seeded in multi-well plates at 7.5 x 10^5 cells/ml in RPMI 1640 medium including 10% FBS. Osteoclast formation is induced with 20 ng/ml of recombinant human receptor activator of NF-kB-ligand (RANKL) and 10 ng/ml of human M-CSF in the presence of various doses of test compounds. After 48 hours of culture, RANKL and M-CSF is replenished and further cultured for 2 days. Then, the cultured cells are stained for tartrate-

resistant acid phosphatase (TRAP). Osteoclasts are identified as TRAP-positive cells with more than 3 nuclei. Total cell viability is assessed by CCK-8 assay (Dojindo, Gaithersburg, Md) with 24 hour incubation.

OTHER EMBODIMENTS

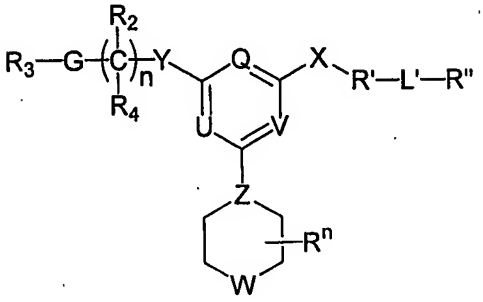
All of the features, specific embodiments and particular substituents disclosed herein may be combined in any combination. Each feature, embodiment or substituent disclosed in this specification may be replaced by an alternative feature, embodiment or substituent serving the same, equivalent, or similar purpose. In the case of chemical compounds, specific values can be combined in any combination resulting in a stable structure. Furthermore, specific values (whether preferred or not) for substituents in one type of chemical structure may be combined with values for other substituents (whether preferred or not) in the same or different type of chemical structure. Thus, unless expressly stated otherwise, each feature, embodiment or substituent disclosed is only an example of a generic series of equivalent or similar features feature, embodiments or substituents.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. For example, compounds structurally analogous a heteroaryl hydrazone compound described in the specification also can be made, screened for their inhibiting IL-12 activities, and used to practice this invention. Thus, other embodiments are also within the claims.

CLAIMS

What is claimed is:

1. A compound of formula (I):



or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, prodrug or polymorph thereof

wherein,

each Q, U, and V are independently N or CR^g, wherein at least one of Q, U, or V is N;

Z is N or CH;

W is O, S, S(O), $S(O)_2$, NR^m, or $NC(O)R^m$, wherein R^m is independently H, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or alkylcarbonyl;

X is $-C(R^g)=N-A-$, wherein A is O, S, S(O), $S(O_2)$, $C(CR^g)_2$, or NR^k;

R' is an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, or absent;

L' is O, S, $N(R^k)$, $N(R^k)C(O)$, $C(O)N(R^k)$, C(O)O, or OC(O), or absent; and

R" is H, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $N(R^k)(CH_2)_nR^g$, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, $-C(O)R^c$, $-C(S)R^c$, $-C(NR)R^c$, halo, haloalkyl, aminoalkyl, mercaptoalkyl, cyano, nitro, $-S(O)R^c$, $-S(O)_2R^c$, $-P(O)R^cR^c$, $-P(S)R^cR^c$, or an optionally substituted alkylcarbonylalkyl;

Y is $(CH(R^g))_m$, C(O), C(NR), O, S, S(O), $S(O)_2$, $N(R^k)$, or absent,

R, for each occurrence, is independently H, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $-C(O)R^c$, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, nitro, cyano, haloalkyl, aminoalkyl, or $-S(O)_2R^c$;

R_3 is R^g, $-C(O)R^c$, $-OC(O)R^c$, $-SC(O)R^c$, $-NR^kC(O)R^c$, $-C(S)R^c$, $-OC(S)R^c$, $-SC(S)R^c$, $-NR^kC(S)R^c$, $-C(NR)R^c$, $-OC(NR)R^c$, $-SC(NR)R^c$, $-NR^kC(NR)R^c$, $-SO_2R^c$, $-S(O)R^c$, $-NR^kSO_2R^c$, $-OS(O)_2R^c$, $-OP(O)R^cR^c$, or $-P(O)R^cR^c$;

R_2 and R_4 for each occurance, are independently, H, an optionally substituted alkyl, an optionally substituted alkylcarbonyl, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, $-C(O)R^c$, $-OC(O)R^c$, $-SC(O)R^c$, $-NR^kC(O)R^c$, $-C(S)R^c$, $-OC(S)R^c$, $-SC(S)R^c$, $-NR^kC(S)R^c$, $-C(NR)R^c$, $-OC(NR)R^c$, $-SC(NR)R^c$, $-NR^kC(NR)R^c$, $-SO_2R^c$, $-S(O)R^c$, $-NR^kSO_2R^c$, $-OS(O)_2R^c$, $-OP(O)R^cR^c$, $-P(O)R^cR^c$, halo, haloalkyl, aminoalkyl, mercaptoalkyl, cyano, nitro, nitroso, azide, an optionally substituted alkylcarbonylalkyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted aralkyl, an optionally substituted heteroaryl, an optionally substituted heteroaralkyl, or isothionitro; or R_2 and R_4 taken together are =O, =S, or =NR;

R^c and R^d, for each occurrence, are independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl, haloalkyl, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, alkylcarbonylalkyl, mercaptoalkyl, aminoalkyl, sulfonylalkyl, sulfonylaryl, or thioalkoxy;

R^g, for each occurrence, is independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl, haloalkyl, $-OR^k$, $-SR^k$, $-NR^hR^j$, hydroxylalkyl, alkylcarbonylalkyl, mercaptoalkyl, aminoalkyl, sulfonylalkyl, sulfonylaryl, thioalkoxy, $-C(O)R^c$, $-OC(O)R^c$, $-SC(O)R^c$, $-NR^kC(O)R^c$, $-C(S)R^c$, $-OC(S)R^c$, $-SC(S)R^c$,$-NR^kC(S)R^c$, $-C(NR)R^c$, $-OC(NR)R^c$, $-SC(NR)R^c$, $-NR^kC(NR)R^c$, $-SO_2R^c$, $-S(O)R^c$, $-NR^kSO_2R^c$, $-OS(O)_2R^c$, $-OP(O)R^cR^c$, $-P(O)R^cR^c$, halo, cyano, nitro, nitroso, or azide;

R^h and R^j, for each occurrence, are independently H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl; or R^h and R^j taken together with the N to which they are attached is an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, or an optionally substituted heteroaryl;

R^k, for each occurrence, is independently H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cyclyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted heterocycloalkyl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, an optionally substituted aryl, an optionally substituted heteroaryl, ;

R^n is –H, alkyl, alkylcarbonyl, halo, nitro, nitroso, cyano, azido, isothionitro, $-OR^p$ or $-SR^p$; and R^p is –H, alkyl, or alkylcarbonyl;

G is:

Hydrazide;
Hydrazone;
Hydrazine;
Hydroxylamine;
Oxime;
Amide;
Ester;
Carbonate;
Carbamate;
Thiocarbamate;
$–NR^k-C(NR)-NR^k-$;
$–NR^k-C(O)-NR^k-$;
$–NR^k-C(S)-NR^k-$;
$-NR^k-S(O)_2-NR^k-$;
Phosphoryl;
an optionally substituted -Cyclyl-;
an optionally substituted -Heterocyclyl-;
an optionally substituted -Aryl-;
an optionally substituted -Heteroaryl-;
an optionally substituted -Heteroarylalkyl-;

an optionally substituted -Heteroaryl-NR^k-;

an optionally substituted -Heteroaryl-S-;

an optionally substituted -Heteroarylalkyl-O-;

$-Si(OR^k)_2$-;

$-B(OR^k)$-

$-C(NR)-NR^k$-;

$-N(R^k)-CR^gR^g-C(O)$-;

$-C(O)-ON(R^k)$-;

$-C(O)-N(R^k)O$-;

$-C(S)-ON(R^k)$-;

$-C(S)-N(R^k)O$-;

$-C(N(R^k))-ON(R^k)$-;

$-C(N(R^k))-NR^kO$-;

$-OS(O)_2-N(R^k)N(R^k)$-;

$-OC(O)-N(R^k)N(R^k)$-;

$-OC(S)-N(R^k)N(R^k)$-;

$-OC(N(R^k))-N(R^k)N(R^k)$-;

$-N(R^k)N(R^k)S(O)_2O$-;

$-N(R^k)N(R^k)C(S)O$-;

$-N(R^k)N(R^k)C(N(R^k))O$-;

$-OP(O)(R^c)O$-;

$-N(R^k)P(O)(R^c)O$-;

$-OP(O)(R^c)N(R^k)$-;

$-N(R^k)P(O)(R^c)N(R^k)$-;

$-P(O)(R^c)O$-;

$-P(O)(R^c)N(R^k)$-;

$-N(R^k)P(O)(R^c)$-;

$-OP(O)(R^c)$-;

-O-alkyl-heterocyclyl-$N(R^k)$-;

$-N(R^k)CHR^gC(O)N(R^k)CHR^gC(O)$-;

$-N(R^k)CHR^gC(O)$-;

$-N(R^k)C(O)CHR^g-$;

$-C(O)N(R^k)CHR^gC(O)-$;

each of which is optionally substituted;

or absent,;

m, for each occurrence, is independently 1, 2, 3, 4, 5, 6, 7, or 8;

n, for each occurrence, is independently 0, 1, 2, 3, 4, 5, 6, or 7; and

p, for each occurrence, is independently 0, 1, or 2.

2. The compound of claim 1, wherein Q, U, and V each are N.

3. The compound of claim 1, wherein two of Q, U and V are N, and the other is CR^g.

4. The compound of claim 3, wherein Q and U each are N and V is CR^g.

5. The compound of claim 3, wherein U and V are N, and Q is CR^g.

6. The compound of claim 3, wherein Q and V are N and U is CR^g.

7. The compound of claim 1, wherein one of Q, U and V is N, and the other two are each CR^g.

8. The compound of claim 7, wherein U is N and Q and V each are CR^g.

9. The compound of claim 7, wherein Q is N and U and V each are CR^g.

10. The compound of claim 7, wherein V is N and Q and U each are CR^g.

11. The compound of claim 1, wherein Y is absent, O, S, $N(R^k)$, or CH_2, and n is 0, 1, 2, 3, or 4.

12. The compound of claim 1, wherein R_3 is an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl, nitro, cyano, halo, OR^k, SR^k, or NR^hR^j.

13. The compound of claim 12, wherein R_3 is optionally substituted aryl or optionally substituted heteroaryl.

14. The compound of claim 13, wherein R_3 is an optionally substituted phenyl, an optionally substituted naphthyl, an optionally substituted anthracenyl, an optionally substituted fluorenyl, an optionally substituted indenyl, an optionally substituted azulenyl, an optionally substituted pyridyl, an optionally substituted 1-oxo-pyridyl, an optionally substituted furanyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted benzo[1,4]dioxinyl, an optionally substituted thienyl, an optionally substituted pyrrolyl, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted thiazolyl, an optionally substituted isoxazolyl, an optionally substituted quinolinyl, an optionally substituted pyrazolyl, an optionally substituted isothiazolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted triazinyl, an optionally substituted triazolyl, an optionally substituted thiadiazolyl, an optionally substituted isoquinolinyl, an optionally substituted indazolyl, an optionally substituted benzoxazolyl, an optionally substituted benzofuryl, an optionally substituted indolizinyl, an optionally substituted imidazopyridyl, an optionally substituted tetrazolyl, an optionally substituted benzimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzothiadiazolyl, an optionally substituted benzoxadiazolyl, an optionally substituted indolyl, an optionally substituted tetrahydroindolyl, an optionally substituted azaindolyl, an optionally substituted indazolyl, an optionally substituted imidazopyridyl, an optionally substituted quinazolinyl, an optionally

substituted purinyl, an optionally substituted pyrrolo[2,3]pyrimidinyl, an optionally substituted pyrazolo[3,4]pyrimidinyl, or an optionally substituted benzo(b)thienyl.

15. The compound of claim 12, wherein R_3 is an optionally substituted heterocycloalkyl.

16. The compound of claim 15, wherein R_3 is an optionally substituted piperidinyl, an optionally substituted piperazinyl, an optionally substituted 2-oxopiperazinyl, an optionally substituted 2-oxopiperidinyl, an optionally substituted 2-oxopyrrolidinyl, an optionally substituted 4-piperidonyl, an optionally substituted tetrahydropyranyl, an optionally substituted oxazolidinyl, an optionally substituted 2-oxo-oxazolidinyl, an optionally substituted tetrahydrothiopyranyl, an optionally substituted tetrahydrothiopyranyl sulfone, an optionally substituted morpholinyl, an optionally substituted thiomorpholinyl, an optionally substituted thiomorpholinyl sulfoxide, an optionally substituted thiomorpholinyl sulfone, an optionally substituted 1,3-dioxolanyl, an optionally substituted [1,4]dioxanyl, an optionally substituted 2-oxo-imidazolidinyl, tetrahydrofuranyl, or an optionally substituted tetrahydrothienyl.

17. The compound of claim 1, wherein R_3 is OR^k, SR^k, $C(O)OR^k$, NR^hR^j, or $C(O)NR^hR^j$.

18. The compound of claim 17, wherein R_3 is $-OR^k$, $-C(O)R^c$, $-OC(O)R^c$, $-NR^kC(O)R^c$ or $-NR^hR^j$, and R^k, R^h and R^j are each, independently, H, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, or an optionally substituted heterocycloalkyl.

19. The compound of claim 1, wherein G is absent.

20. The compound of Claim 1, wherein G is $-C(N\text{-}OH)-$, $-NR^kC(O)-$, $-C(O)NR^k-$, $-OC(O)-$, $-C(O)O-$, $-OC(O)O-$, $-NR^kC(O)O-$, $-OC(O)NR^k-$, $-NR^kC(S)O-$, $-OC(S)NR^k-$, $-NR^kC(NR)NR^k-$, $-NR^kC(O)NR^k-$, $-NR^kC(S)NR^k-$, $-NR^kS(O)_2NR^k-$, $-C(NR)NR^k-$, or $-NR^kCR^gR^gC(O)-$.

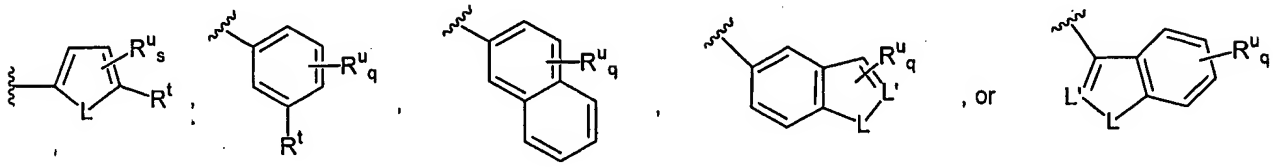
21. The compound of claim 1, wherein Z is N and W is O.

22. The compound of Claim 1, wherein R" is an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cyclyl, an optionally substituted heterocycloalkyl, an optionally substituted heterocyclyl,

23. The compound of Claim 22, wherein R" is an optionally substituted aryl or an optionally substituted heteroaryl.

24. The compound of claim 23, wherein R" is an optionally substituted phenyl, an optionally substituted naphthyl, an optionally substituted anthracenyl, an optionally substituted fluorenyl, an optionally substituted indenyl, an optionally substituted azulenyl, an optionally substituted pyridyl, an optionally substituted 1-oxo-pyridyl, an optionally substituted furanyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted benzo[1,4]dioxinyl, an optionally substituted thienyl, an optionally substituted pyrrolyl, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted thiazolyl, an optionally substituted isoxazolyl, an optionally substituted quinolinyl, an optionally substituted pyrazolyl, an optionally substituted isothiazolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted triazinyl, an optionally substituted triazolyl, an optionally substituted thiadiazolyl, an optionally substituted isoquinolinyl, an optionally substituted indazolyl, an optionally substituted benzoxazolyl, an optionally substituted benzofuryl, an optionally substituted indolizinyl, an optionally substituted imidazopyridyl, an optionally substituted tetrazolyl, an optionally substituted benzimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzothiadiazolyl, an optionally substituted benzoxadiazolyl, an optionally substituted indolyl, an optionally substituted tetrahydroindolyl, an optionally substituted azaindolyl, an optionally substituted indazolyl, an optionally substituted imidazopyridyl, an optionally substituted quinazolinyl, an optionally substituted purinyl, an optionally substituted pyrrolo[2,3]pyrimidinyl, an optionally substituted pyrazolo[3,4]pyrimidinyl, or an optionally substituted benzo(b)thienyl.

25. The compound of claim 24, wherein R' and L' are absent and R" is



wherein:

L is NR^i, O, or S;

L' is N or CR^i;

R^t is H, halogen, CN, an optionally substituted alkyl, an optionally substituted cyclyl, an optionally substituted alkyloxy, an optionally substituted alkylcarbonyl, an optionally substituted alkyloxycarbonyl, an optionally substituted aryloxycarbonyl, an optionally substituted heteroaryloxycarbonyl, hydroxyalkyl, an optionally substituted alkylamino, an optionally substituted dialkylamino, aminocarbonyl, or alkylaminocarbonyl;

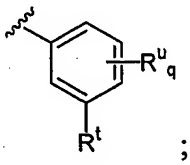
R^u,for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$;

R^i is H, alkyl, or alkylcarbonyl;

s is 0, 1, or 2; and

q is 0, 1, 2, 3, or 4.

26. The compound of claim 25, wherein R' and L' are absent and R" is



wherein

R^t is H, halogen, CN, alkyl, cyclyl, alkyloxy, alkylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, alkylamino, aminocarbonyl, or alkylaminocarbonyl;

R^u, for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$; and

q is 0, 1, 2, 3, or 4.

27. The compound of claim 1, wherein A is O or NR^k.

28. The compound of claim 27, wherein A is NR^k; and R^k is H, methyl, ethyl, or acetyl.

29. The compound of claim 28, wherein R^k is H.

30. The compound of claim 29, wherein Z is N and W is O.

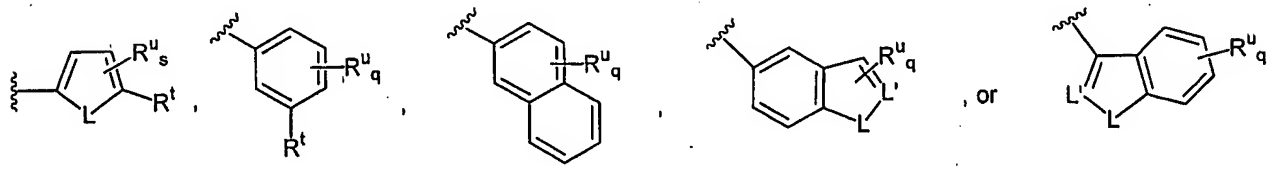
31. The compound of claim 29, wherein Y is absent, O, S, NH, $N(CH_3)$, or CH_2, and n is 0, 1, 2, 3, or 4.

32. The compound of claim 31, wherein Y is O and n is 2.

33. The compound of claim 32, wherein R_3 is an optionally substituted aryl or an optionally substituted heteroaryl.

34. The compound of claim 33, wherein R_3 is pyridinyl, 1-oxy-pyridinyl, 1*H*-pyridin-2-one, moropholin-4-yl, 4-methyl-piperazin-1-yl, or 2-oxo-oxazolidin-3-yl.

35. The compound of claim 27, wherein R' and L' are absent and R" is



wherein:

L is NR^i, O, or S;

L' is N or CR^j;

R^t is H, halogen, CN, an optionally substituted alkyl, an optionally substituted cyclyl, an optionally substituted alkyloxy, an optionally substituted alkylcarbonyl, an optionally substituted alkyloxycarbonyl, an optionally substituted aryloxycarbonyl, an optionally substituted heteroaryloxycarbonyl, hydroxyalkyl, an optionally substituted alkylamino, an optionally substituted dialkylamino, aminocarbonyl, or alkylaminocarbonyl;

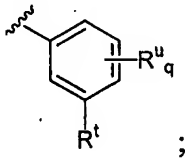
R^u,for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$;

R^i is H, alkyl, or alkylcarbonyl;

s is 0, 1, or 2; and

q is 0, 1, 2, 3, or 4.

36. The compound of claim 35, wherein R' and L' are absent and R" is



;

wherein

R^t is H, halogen, CN, alkyl, cyclyl, alkyloxy, alkylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, alkylamino, aminocarbonyl, or alkylaminocarbonyl;

R^u, for each occurrence, is independently H, halogen, NO_2, CN, alkyl, aryl, heteroaryl, OR^k, $OC(O)R^c$, SO_2R^c, $S(O)R^c$, $S(O_2)NR^hR^j$, SR^k, NR^hR^j, NR^kCOR^c, $NR^kC(O)OR^c$, $NR^kC(O)NR^hR^j$, $NR^kSO_2R^c$, COR^c, $C(O)OR^c$, or $C(O)NR^hR^j$; and

q is 0, 1, 2, 3, or 4.

37. The compound of claim 36, wherein R^t is CH_3, Cl, or OCH_3.

38. The compound of claim 37, wherein R^u is H or CH_3 and q is 1.

39. The compound of claim 29, wherein each of of Q, U and V is, independently, N or CH, provided that at least one of Q, U, and V is N;

40. The compound of claim 39, wherein two of Q, U and V are N, and the other is CH.

41. The compound of claim 40, wherein Q and U each are N and V is CH.

42. The compound of claim 40, wherein U and V are N, and Q is CH.

43. The compound of claim 40, wherein Q and V are N and Q is CH.

44. The compound of claim 1, wherein the compound is selected from:

1: *N*-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-*N*'-*m*-tolyl-hydrazine;

2: *N*-(3-Chloro-phenyl)- *N*'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine;

3: *N*-(3-Methoxy-phenyl)- *N*'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine;

4: *N*-(2,5-Dimethyl-phenyl)- *N*'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]- hydrazine;

5: 1-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

6: N-[2-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-m-tolyl-hydrazine;

7: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-N'-m-tolyl-hydrazine;

8: N-[6-Morpholin-4-yl-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-m-tolyl-hydrazine;

9: 3-{2-[4-Morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-2-yloxy]-ethyl}-oxazolidin-2-one;

10: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-N'-m-tolyl-hydrazine;

11: 3-{2-[4-Morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyridin-2-yloxy]-ethyl}-oxazolidin-2-one;

12: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-m-tolyl-hydrazine;

13: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-m-tolyl-hydrazine;

14: 3-{2-[4-Morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-ethyl}-oxazolidin-2-one;

15: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-m-tolyl-hydrazine;

16: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-m-tolyl-hydrazine;

17: 3-{2-[6-Morpholin-4-yl-2-(m-tolyl-hydrazonomethyl)-pyrimidin-4-yloxy]-ethyl}-oxazolidin-2-one;

18: Methyl-{2-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-2-yloxy]-ethyl}-amine;

19: Methyl-{2-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyridin-2-yloxy]-ethyl}-amine;

20: 2-Methyl-1-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-2-yloxy]-propan-2-ol;

21: 2-Methyl-1-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyridin-2-yloxy]-propan-2-ol;

22: 2-Methyl-1-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-2-yloxy]-propan-2-ol;

23: 2-Methyl-1-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyridin-2-yloxy]-propan-2-ol;

24: Methyl-{2-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-ethyl}-amine;

25: Methyl-{2-[6-morpholin-4-yl-2-(m-tolyl-hydrazonomethyl)-pyrimidin-4-yloxy]-ethyl}-amine;

26: 2-Methyl-1-[4-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-propan-2-ol;

27: 2-Methyl-1-[2-morpholin-4-yl-6-(m-tolyl-hydrazonomethyl)-pyrimidin-4-yloxy]-propan-2-ol;

28: -Methyl-1-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-propan-2-ol;

29: 2-Methyl-1-[2-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-4-yloxy]-propan-2-ol;

30: N-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

31: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

32: N-[6-Morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

33: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

34: Methyl-{2-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-2-yloxy]-ethyl}-amine;

35: Methyl-{2-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyridin-2-yloxy]-ethyl}-amine;

36: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

37: N-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

38: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

39: N-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-N'-naphthalen-2-yl-hydrazine;

40: Methyl-{2-[4-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-[1,3,5]triazin-2-yloxy]-ethyl}-amine;

41: Methyl-{2-[2-morpholin-4-yl-6-(naphthalen-2-yl-hydrazonomethyl)-pyrimidin-4-yloxy]-ethyl}-amine;

42: N-(1H-Indol-3-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

43: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

44: N-(1H-Indol-3-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

45: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

46: (2-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

47: (2-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

48: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

49: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

50: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

51: N-(1H-Indol-3-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

52: (2-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

53: (2-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

54: 1-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

55: 1-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

56: 1-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

57: 1-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

58: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

59: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

60: 1-{4-[(1H-Indol-3-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

61: 1-{6-[(1H-Indol-3-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

62: 1-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

63: 1-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

64: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

65: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

66: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

67: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

68: (2-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

69: (2-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

70: 3-{N'-[2-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

71: 3-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-benzamide;

72: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

73: N-(2,3-Dimethyl-1H-indol-5-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

74: (2-{4-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

75: (2-{6-[(2,3-Dimethyl-1H-indol-5-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

76: 3-{N'-[4-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

77: 3-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

78: 3-{N'-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

79: 3-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-benzamide;

80: 3-{N'-[6-Morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

81: 3-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-benzamide;

82: 3-{N'-[2-(2-Methylamino-ethoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

83: 3-{N'-[6-(2-Methylamino-ethoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-benzamide;

84: 3-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

85: 3-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-benzamide;

86: 3-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

87: 3-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-benzamide;

88: 3-{N'-[4-(2-Methylamino-ethoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-benzamide;

89: 3-{N'-[6-(2-Methylamino-ethoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-benzamide;

90: 4-Methyl-2-{N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

91: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenylamine;

92: 4-Methyl-2-{N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

93: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenylamine;

94: 4-Methyl-2-{N'-[2-(2-methylamino-ethoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

95: 4-Methyl-2-{N'-[6-(2-methylamino-ethoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-phenylamine;

96: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenylamine;

97: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenylamine;

98: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenylamine;

99: 4-Methyl-2-{N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenylamine;

100: 4-Methyl-2-{N'-[4-(2-methylamino-ethoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenylamine;

101: 4-Methyl-2-{N'-[6-(2-methylamino-ethoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenylamine;

102: 1-{4-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

103: 1-{6-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

104: N-(5-Ethyl-thiophen-2-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

105: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

106: N-(5-Ethyl-thiophen-2-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

107: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

108: 1-{4-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

109: 1-{6-[(2-Amino-5-methyl-phenyl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

110: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

111: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

112: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

113: N-(5-Ethyl-thiophen-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

114: (2-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

115: (2-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

116: 1-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

117: 1-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

118: N-(4,5-Dimethyl-furan-2-yl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

119: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

120: (2-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

121: (2-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

122: 1-{4-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

123: 1-{6-[(5-Ethyl-thiophen-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

124: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

125: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

126: N-(4,5-Dimethyl-furan-2-yl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

127: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

128: (2-{4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

129: (2-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

130: 1-{4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

131: 1-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

132: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

133: N-(4,5-Dimethyl-furan-2-yl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

134: (2-{4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

135: (2-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

136: {4-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol;

137: 1-{6-[(4,5-Dimethyl-furan-2-yl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-2-methyl-propan-2-ol;

138: 4-{N'-[6-Morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

139: 4-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenol;

140: 4-{N'-[6-Morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

141: 4-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazino}-phenol;

142: 4-{N'-[2-(2-Methylamino-ethoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

143: 4-{N'-[6-(2-Methylamino-ethoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-phenol;

144: 4-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

145: 4-{N'-[4-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenol;

146: 4-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

147: 4-{N'-[4-Morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazino}-phenol;

148: 4-{N'-[4-(2-Methylamino-ethoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

149: 4-{N'-[6-(2-Methylamino-ethoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

150: 4-{N'-[2-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

151: 4-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-4-morpholin-4-yl-pyridin-2-ylmethylene]-hydrazino}-phenol;

152: N-(3,4-Dimethyl-phenyl)-N'-[6-morpholin-4-yl-2-(2-pyridin-2-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

153: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

154: N-(3,4-Dimethyl-phenyl)-N'-[6-morpholin-4-yl-2-(2-piperidin-1-yl-ethoxy)-pyrimidin-4-ylmethylene]-hydrazine;

155: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyridin-2-ylmethylene]-hydrazine;

156: 4-{N'-[4-(2-Hydroxy-2-methyl-propoxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethylene]-hydrazino}-phenol;

157: 4-{N'-[6-(2-Hydroxy-2-methyl-propoxy)-2-morpholin-4-yl-pyrimidin-4-ylmethylene]-hydrazino}-phenol;

158: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

159: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

160: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-[1,3,5]triazin-2-ylmethylene]-hydrazine;

161: N-(3,4-Dimethyl-phenyl)-N'-[4-morpholin-4-yl-6-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-ylmethylene]-hydrazine;

162: (2-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-ethyl)-methyl-amine;

163: (2-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-ethyl)-methyl-amine;

164: 1-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-pyrimidin-2-yloxy}-2-methyl-propan-2-ol;

165: 1-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-4-morpholin-4-yl-pyridin-2-yloxy}-2-methyl-propan-2-ol;

166: (2-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-ethyl)-methyl-amine;

167: (2-{6-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-2-morpholin-4-yl-pyrimidin-4-yloxy}-ethyl)-methyl-amine;

168: 1-{4-[(3,4-Dimethyl-phenyl)-hydrazonomethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy}-2-methyl-propan-2-ol.

45. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim1.

46. A method for treating an interleukin-12 overproduction-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

47. The method of Claim 46, wherein the disorder is selected from the group consisting of multiple sclerosis, sepsis, myasthenia gravis, autoimmune neuropathies, Guillain-Barré syndrome, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, psoriatic arthritis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, ulcerative colitis, interstitial

pulmonary fibrosis, myelofibrosis, hepatic fibrosis, myocarditis, thyroditis, primary biliary cirrhosis, autoimmune hepatitis, immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland; rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, spondyloarthropathies, ankylosing spondylitis, Sjogren's syndrome and graft-versus-host disease.

48. The method of claim 47, wherein the disorder is rheumatoid arthritis, sepsis, Crohn's disease, multiple sclerosis, psoriasis, or immune-mediated diabetes mellitus.

49. A method of inhibiting IL-12 production in a subject, comprising administering to the subject an effective amount of a compound of claim 1.

50. A method of inhibiting the proliferation of T_H1 lymphocytes in a subject, comprising administering to the subject an effective amount of a compound of claim 1.

51. A method for treating or preventing disorders associated with excessive bone loss, the method comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

52. The method of claim 51, wherein the disorder is periodontal disease, non-malignant bone disorders, osteoporosis, Paget's disease of bone, osteogenesis imperfecta, fibrous dysplasia, and primary hyperparathyroidism, estrogen deficiency, inflammatory bone loss, bone malignancy, arthritis, osteopetrosis, hypercalcemia of malignancy (HCM), osteolytic bone lesions of multiple myeloma and osteolytic bone metastases of breast cancer, and metastatic cancers.

53. A method for inhibiting osteoclast formation *in vitro* or *in vivo*, the method comprising contacting a pre-osteoclast cell with an effective amount of a compound of claim 1.

54. A method of treating or preventing a disorder associated with excessive bone resorption by osteoclasts in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of claim 1.

55. A method of inhibiting IL-23 production in a subject, comprising administering to the subject an effective amount of a compound of claim 1.

56. The method of Claim 55, further comprising inhibiting the production of IL-12.

57. A method of inhibiting IL-27 production in a subject, comprising administering to the subject an effective amount of a compound of claim 1.

58. The method of Claim 57, further comprising inhibiting TH1 lymphocyte proliferation.

59. The method of Claim 58, further comprising inhibiting the production of IL-12.

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